THE American Journal OF Gastroenterology

VOL. 35, NO. 5 MAY, 1961

Drugs and the Gastroenterologist

The Role of Salicylates in Massive Gastrointestinal Hemorrhage

Further Evaluation of Splenic Pulp Manometry as a Differential Diagnostic Test of Acute Upper Gastrointestinal Bleeding

Human Biliary-Pancreatic Secretion

Cinegastroscopy—II. External Source of Light for Color Cinematography Through the Gastroscope

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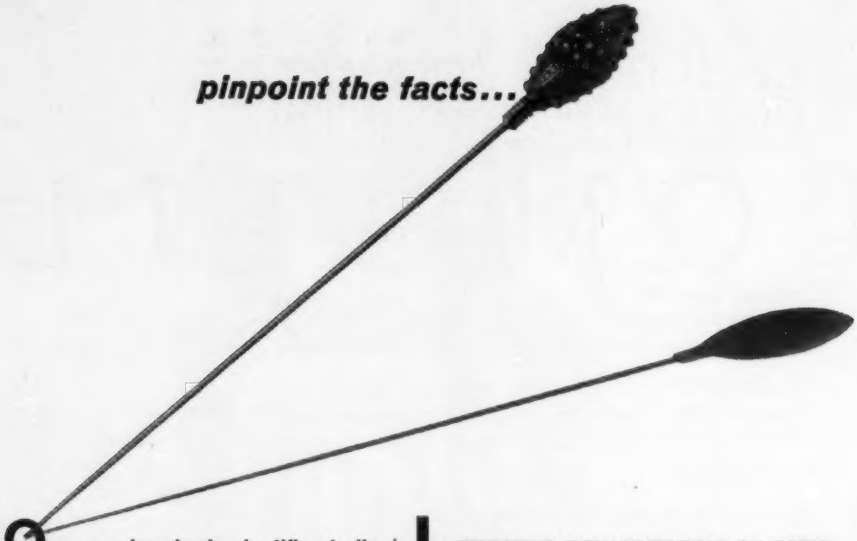

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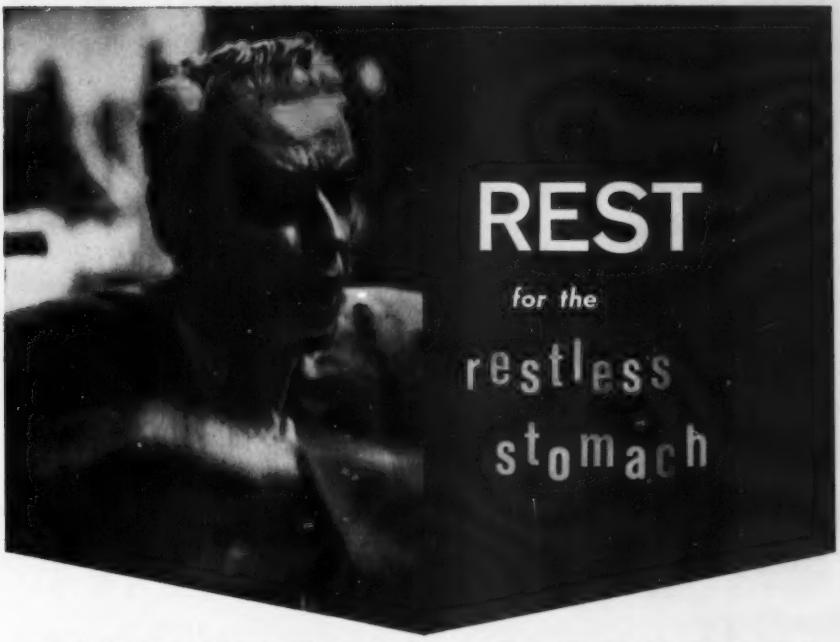

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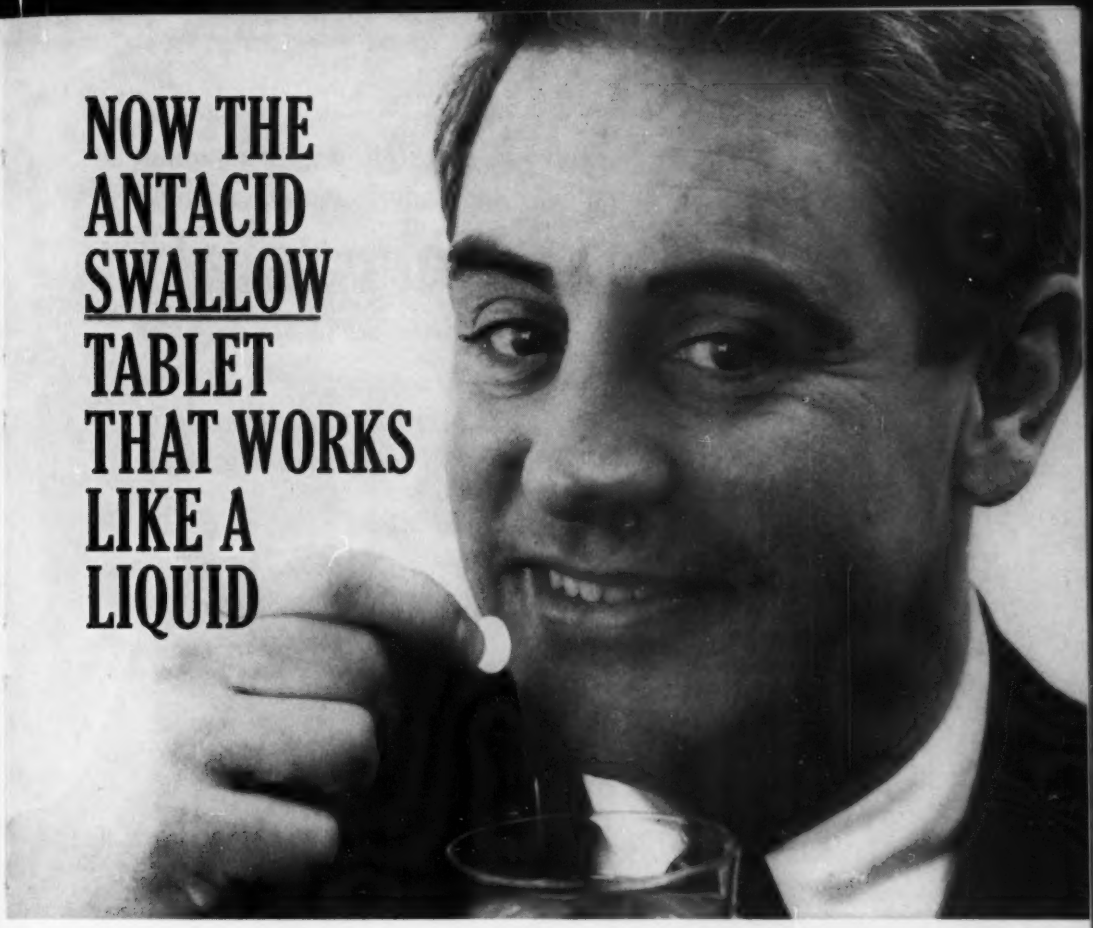

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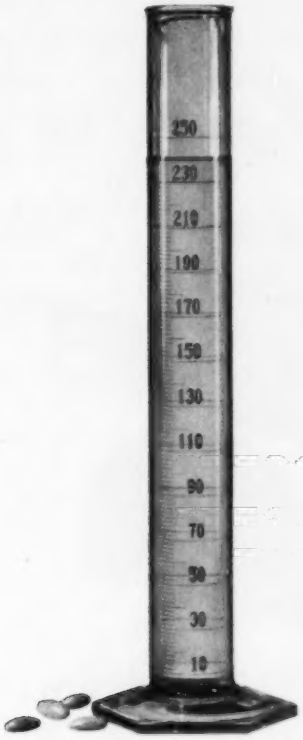

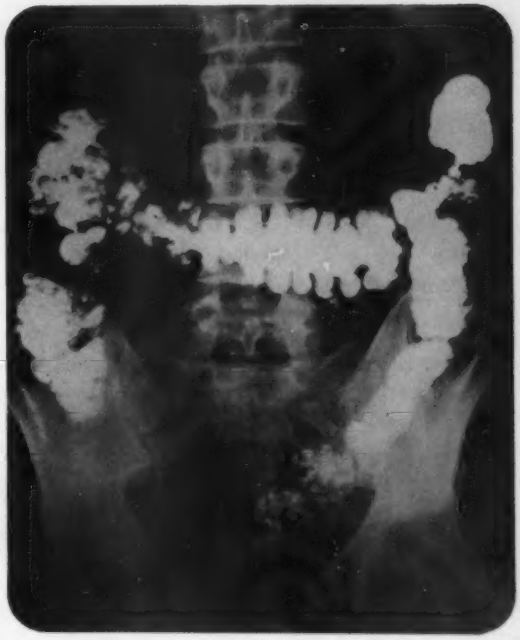

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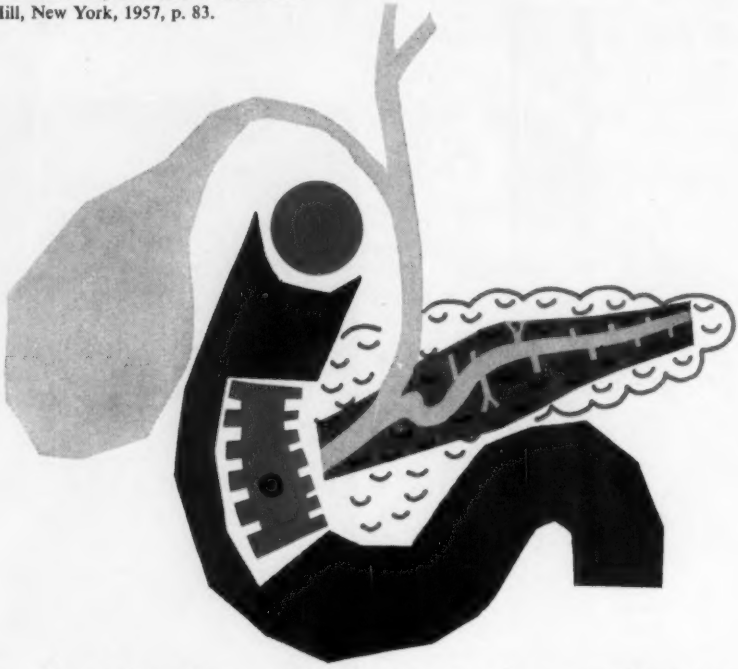

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DRUGS AND THE GASTROENTEROLOGIST*

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The aspects of iatrogeny confronting the gastroenterologist are dual; they relate to the possible untoward effects of his own medication and procedures as well as to the gastrointestinal disorders attributable to therapy of physicians in other fields of medicine. Long-familiar preparations continue to require discrimination and alertness in their common usage. The growth of pharmaceutical chemistry has led and, undoubtedly, will continue to lead to a widening spectrum of iatrogennete processes. Any one newly discovered chemical compound may well become the most efficient medicinal agent against a given disease, but it or its analogues may also initiate other disorders, perhaps more serious than the one for which it was intended. Although the chemist, the pharmacologist, the physiologist, and the clinical investigator cross and re-cross paths in the effort to discover possible harmful effects of new preparations, the lag which is inherent in breadth of usage and depth of time often permits local or system damage to remain undisclosed until long after the release and wide acceptance of a new product.

Many of the factors in iatrogeny are best considered as open or, at most, partially answered questions:

1. Is the *modus operandi* of a secondary, harmful drug effect toxic, hypersensitive, or yet unclassified?

2. Has the ill effect actually been due to the suspected therapeutic agent, or has the trail of events in the natural history of the primary disease (or of another and unsuspected disease) been covered by *post hoc, propter hoc* reasoning?

3. Does a particular agent exert its harmful action

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a. only in excessive dosage, or

b. only upon susceptible individuals, or

c. only after sensitization by itself (or cross-sensitization by a similar agent) and readministration?

4. Is there a practical method by which susceptibility can be avoided predictably?

5. Does a particular drug's potential for harm warrant its projected potential for benefit? Is it worth the physician's assumption of a calculated risk?

In the field of gastroenterology one of the simplest approaches to the subject concerns the involvement of the various segments of the gastrointestinal apparatus.

Stomach and Duodenum

The stomach, in particular, has been the unfortunate target for the untoward effect of numerous drugs in every-day use. A great deal of discussion has centered about the role of the salicylates, especially aspirin, in the etiology of gastric hemorrhage or in the initiation or reactivation of peptic ulcer. This has been approached from several angles. Intubation studies, conducted by Schneider[1], disclosed the presence of blood in gastric aspirate after oral administration of aspirin even though there were no changes in acidity; the administration of aspirin buffered with magnesium oxide, however, was not attended with bleeding. Gastroscopic technics, in the hands of other investigators[2-4] have not always been conclusive; the oral administration of aspirin has generally been followed by gastroscopic visualization of patches of erosive gastritis around adherent particles of the drug. Gastrectomy specimens from peptic ulcer subjects who had been given aspirin preoperatively showed a high incidence of acute erosive gastritis around adherent particles of the medication[5]. Levrat and Lambert[6], after intensive clinical study, concluded that "acetylsalicylic acid has a corrosive effect on the gastric contents, all the more so in that the insoluble particles of the drug come into direct contact with the mucosa". Their report included a number of instances of isolated hemorrhage following the use of aspirin; in most cases no demonstrable organic lesion could be found. Similar reports of occult bleeding and of frank hematemesis and melena have been made by Lange[7,8]. Matsumoto and Grossman[9] found a significant rise in fecal blood loss as determined by fecal radioactivity after administration of Cr^{51}-tagged erythrocytes during a course of aspirin. While these hemorrhagic phenomena seem particularly apt to occur in elderly patients who have taken salicylates over a long period of time, they have been found also after single large doses or after relatively small quantities taken by known ulcer patients or by otherwise susceptible individuals of any age.

Among other drugs employed in rheumatology, phenylbutazone has been implicated in the etiology of peptic ulcer, gastritis, gastric mucosal irritation and upper gastrointestinal bleeding. Mauer[10] found 40 proven cases of peptic ulcer and over 400 cases of gastrointestinal symptomatology suggestive of organic disease in some 4,000 instances of use of the drug. Experimental studies in the pathogenesis of these effects have been inconclusive; the effect of the drug on gastric secretion has varied according to mode of administration and type of subject. While there is no agreement as to the mode of action[11], its implication in the etiology and re-activation of peptic ulcer and its role in the occurrence of isolated hemorrhage has been well documented.

Similarly, steroid therapy is generally conceded to be potentially ulcerogenic. Kirsner's group[12] has implied that the steroids have been needlessly accused in this connection, and has adduced apparently convincing statistical evidence in support of this view. On the other hand, Kern, Lukens and Clark[13] studied the incidence of peptic ulcer in patients with rheumatoid arthritis, found a relative increase in frequency, and concluded that this increase was significantly related to treatment with adrenocortical hormones and phenylbutazone. Belief in the relative security of the newer drugs cannot be shared by Adelman and Zaslow[14], who cited instances prior to their own reported case of acute perforation of a newly-formed peptic ulcer after only 900 mg. of phenylbutazone. In my own experience there is the instance of a 68-year old female who developed massive melena in 1955 during administration of cortisone acetate, and a similar episode of severe melena in 1960 after taking 1.2 gm. of phenylbutazone over a five-day period; on neither occasion was any organic lesion of the upper gastrointestinal tract demonstrated radiologically within four days after the hemorrhage. Again, although there is a dossier of documentation for the reactivation of peptic ulcer by steroids, there is no agreement as to pathogenesis. Theoretical considerations range from those involving increase in gastric hydrochloric acid and pepsin concentration with marked reduction in the viscosity and content of visible mucus[15], through stimulation of gastric secretion by proteolytic enzymes[16], to Halme's[17] suggestion concerning changes in gastric mucoprotein secretion as affected by its competition with other functions which might be monopolized by specific medication.

The rauwolfia group has also been accused of the production or reactivation of peptic ulcer. As in the case of the steroids, the masking effect of the euphoria which often accompanies their use has been thought to compound the risk. Acute hemorrhagic gastritis[18], apparent reactivation of duodenal ulcer disease[19], fresh peptic ulcer[20], all have been described. For the most part, these phenomena have followed either large doses or parenteral administration, but acute gastrointestinal bleeding has occurred after lengthy use of small doses of reserpine. This is another instance in which the pathogenesis of the untoward response remains unsettled. To quote Duncan and Fleeson[21], however, "It is most improb-

able that gastrointestinal bleeding in patients taking reserpine is simply a fortuitous occurrence".

Even more recently the employment of an old drug in a new field, that of nicotinic acid in the treatment of hypercholesteremia, has been reported in the activation of peptic ulcer[22]. Here it appears that simple cessation of therapy is enough to permit healing, or buffering of the drug will prevent harmful activity.

The clinician's watchfulness over potential side-effects of therapy must still include the older, well-established modes. It remains necessary to guard against oversedation in peptic ulcer disease, especially in view of the impact of barbiturates upon the functionally impaired liver seen in about one-third of ulcer patients. The risk of bowel or bladder stasis, or of exacerbation of a concomitant glaucoma, inherent in the use of spasmolytic or anticholinergic drugs, particularly in the elderly, is not insignificant. Certain of the newer anticholinergics seem to have minimized this danger, at least when restricted to minimal effectual dosages. Although alkaline powders have generally been superseded by the absorption or buffering of gastric acid, the syndrome of alkalosis originally recognized by Sippy still occurs[23]. Even the neutralizing gels can be hazardous when administered during or early after gastrointestinal bleeding; a mass, concocted of the gel and the degradation products of blood, is capable of producing intestinal obstruction of a grade requiring surgical intervention.

Hepatobiliary Tract

Pharmaceuticals have been known to cause harmful, often fatal, reactions in the hepatobiliary system for more than 30 years, since the development of arsenical compounds for the parenteral treatment of syphilis and benzene-ring compounds for use in arthritis. Although many cases of "arsenical hepatitis" reported prior to 1940 were actually viral hepatitis of parenteral origin, there was also a large number of true arsenical hepatitides. In the case of cinchophen and related drugs, the often fatal subacute atrophy has been related to direct chemical hepatotoxicity.

In more recent years the list of hepatobiliary offenders has paralleled the rapid elaboration of new drugs. Aside from the mass of iatrogennete hepatitis caused by virus-infected material introduced parenterally, there is a large group of disorders caused by oral medication. The degree of hepatic damage varies widely, from abnormalities detectable only by deviations in one or two of a battery of function tests to a severity progressing to death. The jaundice produced by these agents is also variable in its pathogenesis; it may be classified into the hepatocellular, the cholangiolytic and the mixed types described by Zimmerman[24].

It seems but a short time since these effects were largely limited to gold compounds, arsenicals, carbon tetrachloride, cinchophen, dinitrophenol and certain of the antiepileptic drugs. Now the list has been vastly enlarged by the

introduction of methyltestosterone, sulfonamides, thiourea compounds, para-aminosalicylic acid, phenylbutazone, chlorpromazine (Thorazine), prochlorperazine (Compazine)[25,26], promazine (Sparine), tolbutamide (Orinase)[27], chlorpropamide (Diabinese), iproniazid (Marsilid), novobiocin, and a host of others in which varying frequencies and degrees of hepatic dysfunction have been encountered.

The incidence of dysfunction is not always a minor one. In 1955, the author participated in a report of three cases of chlorpromazine jaundice[28], then anticipating a more comprehensive study of more than 40 such cases found in some 2,000 patients to whom the drug had been given. Before a full assessment could be made the literature was already full of such reports. Aside from the relatively high incidence, about 2.2 per cent in our series, fatalities have not been rare, and prolonged jaundice and morbidity have often been severe. Brick and Buckley[29] reported three cases of chlorpromazine jaundice of more than three months' duration, and reviewed 30 reports, comprising some 120 cases, in which jaundice persisted more than three months in 12 instances and surgical exploration had been performed in 21 cases. While most evidence has indicated a cholangiolar obstruction as the basis of chlorpromazine jaundice, the precise mechanism has not always appeared to be identical. Waitzkin's recent study[30] may clarify this apparent ambiguity. He postulates a primary acute liver cell injury, probably hepatotoxic, due to a first course of chlorpromazine; this usually subsides spontaneously but may progress to frank jaundice in 1 to 2 per cent of cases. Then, he proposes the probability of hepatic allergy on readministration of the drug after a suitable interval in patients who have become sensitized to it. Not only is his theory well supported by clinical documentation, but he has demonstrated successful desensitization against such allergic reactions. Some drugs, even in the accepted dosages, are more severely hepatotraumatic, whether by toxicity or by hypersensitization, than others. One of the more serious in potentiality is iproniazid[31-33], which is capable of a wide range of hepatic damage, often remarkably rapid in development, reaching to acute or subacute necrosis and death.

Colon

This segment of the alimentary tract, usually receiving only the breakdown products of ingested medication, relatively low in absorptive capacity, and possessed of a built-in ability to reject and expel local irritants, is not prominently involved in iatrogennete drug disorders. ACTH and other steroids used in the treatment of ulcerative colitis have been implicated in the etiology of giant ulceration and perforation of the colon in a number of reports; as in the case of complications of steroid therapy involving the upper gastrointestinal tract, the masking effect of the medication has been stressed. In an extensive critical review by Goldgraber[34] it is recalled that perforation of the colon has always been an infrequent but serious complication of ulcerative colitis, and that cases

with masked symptoms were seen both before and since the use of steroids. On the other hand, it has been the author's unhappy experience during the past seven years to have seen five cases of giant ulceration or perforation while steroid treatment was being employed, none when it was not. Steroids administered in the form of retention enemas or as slow rectal drip have not been found responsible for untoward reactions up to this time. Another agent used extensively in treatment of ulcerative colitis, salicylazopyridine (Azulfidin), has been reported[35] in the etiology of agranulocytosis, perhaps fatal, in isolated cases. The occurrence of postantibiotic pseudomembranous colitis, an uncertain entity in the light of recent literature, cannot be classified as an iatrogennete disorder at this time.

Iatrogeny, however, can be attributed to certain physical agents. With increased use of radiation therapy for abdomino-pelvic malignancy has come the appearance of mucosal ulceration of the small or large intestine and the possibility of perforation of the bowel[36]. In the case of a 38-year old patient seen in 1959, intensive cobalt radiation was followed by the appearance of tarry stools and fresh rectal bleeding; while the source of the tarry material could be traced to the jejunum, the lesion could not be identified radiologically as metastatic or ulcerative; however, sigmoidoscopy demonstrated superficial and deep ulceration of the proximal rectum and sigmoid, histologically nonmalignant, as the source of the bright blood.

Even a nonabsorbable agent, barium, is capable of harm, in this instance as a potential cause of intestinal obstruction. Boreadis and Hermel[37] recently called attention to the frequency of prolonged retention of barium, administered by either the oral or the rectal route, and to the necessity for prompt postprocedural flushing out of this material.

This panorama of iatrogeny in gastroenterology has not touched upon many specific drugs which might be mentioned. It has not entered the field of the ethics or, for that matter, the medicolegal aspects involved in the propagation and prescription of potentially dangerous drugs. It is intended to recall to attention the element of risk in some of the older and many, perhaps most, of the newer preparations. It is an attempt to highlight the need for continued and expanded study of the chemicodynamics and the physiochemical pathology of iatrogeny. It is a plea for the physician's full knowledge of any drug's potential for harm, for his education in these risks in easily readable print, for his self-imposed caution in the prescription of medication, and for his free discussion of projected therapy with the patient, with a view to the discovery of the earliest signs of untoward reaction.

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THE ROLE OF SALICYLATES IN MASSIVE GASTROINTESTINAL HEMORRHAGE*

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A controversy has existed for more than a decade over the role of salicylates in gastrointestinal bleeding. There are those who feel that salicylates could be responsible for the bleeding; those more skeptical who are awaiting additional evidence, and finally the group who ridicules the very idea. Among the latter, one finds an internist as eminent as Dr. Isidore Snapper[1], who emphatically stated before our Postgraduate Course in 1957, that he had never seen a case of hemorrhage from salicylates. Then among those who do believe that this drug can cause bleeding, there is divided opinion between the local gastric irritation theory and the hypothesis that the effect is primarly systemic on blood coagulation. Therefore, there is a great need to clarify and crystallize our thinking concerning the relationship of salicylate administration to gastrointestinal bleeding.

TABLE I

GASTROINTESTINAL HEMORRHAGE

1 July 1959		1 January 1960
	45 cases	
with salicylates	26*	58%
without salicylates	19	42%

*21 (46%) had medication 24 hours before admission.

Although Balz[3] in 1877 was the first to write of gastrointestinal bleeding after salicylate medication, it was Douthwaite and Lintott[4] in 1938 who initially described gastroscopic findings in 16 patients swallowing aspirin. They reported varying degrees of hyperemia, vascular engorgement, and submucosal hemorrhage. Forssell[6] substantiated these observations and, in addition, visualized the drug particles as being gripped by the muscularis mucosa apparently leaving cavities. Paul[7], however, could not find any changes in the mucosa attributed

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to the medication after viewing several hundred patients through the gastroscope. Furthermore, he discredited Forssell stating that the cavities were illusions, merely shadows cast by the particles since they disappeared as the patient was rotated.

More recently attention has been called to the alarmingly high incidence of gastrointestinal hemorrhage following salicylates. Muir and Cossar[8], in 1955, found one-third of 166 patients had taken salicylates within a few hours of bleeding. Within the next few years, Brown and Mitchell[9] reported 41 per cent,

TABLE II

SEX

	Total	Salicylates		No salicylates	
Male	27	17	63%	10	37%
Female	18	9	50%	9	50%

while Alvarez and Summerskill[10] noted that salicylates could be incriminated in over 40 per cent of the massive gastrointestinal bleeders in their series.

F. Avery Jones[11], probably the best known of the British gastroenterologists, concluded that salicylates play a significant part in precipitating gastrointestinal bleeding and may account for 40 per cent of the x-ray negative admissions for hematemesis or melena. Lange's[5] study in Norway similarly left little doubt of the relationship. He considered this to be the prevailing factor in 45 of 96 cases.

TABLE III

AGE

	Total	Salicylates	Nonsalicylates
Range	27-88 years	31-79 years	27 to 88 years
Mean	54.5	55 years	54 years

Levrat and Lambert[12] of France, in a recent publication, reported their experience favoring the thought that salicylates were an irritative factor in precipitating gastrointestinal hemorrhage.

Waterson[13] pointed out that the "aspirin history" was obtained in 151 of 165 patients. In 3 cases there was reasonably good evidence that aspirin caused the bleeding in the absence of any gastrointestinal lesion. He did not, however, attempt to correlate the percentage of cases in which the drug may have played a contributory role in the presence of gastroduodenal pathology.

Muir and Cossar[8] were impressed with the gastrectomy specimens from patients given insoluble aspirin preoperatively, concluding that salicylates produced an erosive gastritis. The routine gastrectomy specimens under similar conditions observed by Alvarez and Summerskill[10], however, were less conclusive, owing to the presence of hemorrhage and acute erosions in control specimens.

A study was undertaken at Touro Infirmary from 1 July 1959 to 1 January 1960 on the relationship of salicylates to gastrointestinal bleeding. One of the most pertinent facts to come out of this study was the importance (so often reiterated and too seldom practiced), of taking an adequate patient history.

The necessity for specific questioning can be emphasized by my own experience with two massive bleeders who were seen a few weeks ago. Both denied

TABLE IV

GASTROINTESTINAL HEMORRHAGE WITH SALICYLATES

X-ray findings		
Active peptic ulcer	10	37%
Hypertrophic gastritis	2	8%
Deformed duodenal bulb	4	16%
Hiatal hernia	1	4%
Normal gastrointestinal series	5	19%
No x-rays taken	4	16%

any and all drug intake until they were reminded by their respective wives that one took Alka Seltzer regularly after meals, while the other could not go to sleep without his two to four aspirins.

The attitude of the average patient is that inquiry is being made about drugs purchased with a prescription. He has found that he can buy a variety of salicylate preparations over the counter. To him, these are innocuous and not really drug preparations. Therefore, it becomes the specific responsibility of the doctor to initiate a direct line of questioning about salicylates.

Table I indicates that 26 of 45 patients gave a positive history of salicylate ingestion. Of these, 21 or 46 per cent had taken medication within 24 hours of the onset of bleeding.

There were 27 males and 18 females (Table II). Sixty-three per cent of the males and 50 per cent of the females took salicylates.

Age revealed no clues (Table III).

From Table IV we find that x-ray, during or after the hemorrhage, revealed active peptic ulcer to be present in 37 per cent while normal gastrointestinal series was recorded in 19 per cent.

The final diagnosis was peptic ulcer in 69 per cent; hemorrhagic gastritis, cause undetermined in 8 per cent; hemorrhagic gastritis due to aspirin 8 per cent; hemorrhage, cause undetermined 15 per cent (Table V).

Comparing our study with those previously mentioned revealed a rather close correlation (Table VI).

This was convincing evidence to us that salicylate administration plays some part in gastrointestinal bleeding. What then was the role?

Before drawing any conclusion, it was deemed necessary to study more thoroughly the most important etiological factor of gastrointestinal hemorrhage independent of salicylates, namely stress.

TABLE V

FINAL DIAGNOSIS
GASTROINTESTINAL HEMORRHAGE WITH SALICYLATES

Peptic ulcer	18	69%
Hemorrhagic gastritis, cause undetermined	2	8%
Hemorrhage secondary to aspirin	2	8%
Cause undetermined	4	15%

Selye[14] demonstrated experimentally that capillary engorgement with minute hemorrhages would occur in the stomach of rats when exposed to various stressors.

In their monograph, "Human Gastric Function" published in 1943, Wolf and Wolff[15] first described ulceration and hemorrhage in the human stomach following emotional stress.

Breckenridge and his coworkers[16] cited the development of acute gastric erosions in six previously eupeptic patients exposed to stress of different types, including trauma, infections, cerebral hemorrhage or operation. Every case was fatal, five dying from hemorrhage. This is consistent with other reports of hemorrhage following stress[17].

It is an apparent and an accepted fact that bleeding from the gastrointestinal tract can emanate from stress factors alone. The hemorrhagic aspects may be considered as part of the nonspecific effects of stress in the production of gastroduodenal ulceration[18], or may well be independent of it.

Why should salicylates even be considered as playing any role in gastrointestinal bleeding? In addition to the previously mentioned clinical observations of massive bleeding, there are many investigators who have been impressed with the occult blood loss from the gastrointestinal tract following salicylate therapy.

Lange[5] revealed that chronic administration of salicylates regardless of solubility or formula was an important cause of occult bleeding. Stubbe's clinical study of rheumatoid arthritics and controls on salicylate therapy reported[19] 70 per cent positive stools for occult blood in both. Barager and Douthie[20] failed to find much evidence that aspirin was that hazardous, and thought that the anemia of the rheumatoid arthritics in 244 patients observed was due to the disease itself. Dixon et al[21], however, employing Cr^{51} measured daily fecal blood loss over a period up to 3 months and found 70 per cent to average 5 ml. loss per

TABLE VI

Authors	Year	No. of gastrointestinal hemorrhages	Per cent with salicylates
Muir and Cossar (Br.)	1955	166	32
Brown and Mitchell (U.S.)	1956	46	41
Lange (Norway)	1957	96	48
Alvarez and Summerskill (Br.)	1958	102	40
Kossover and Kaplan (U.S.)	1960	45	46

day. Matsumoto and Grossman[22] confirmed these observations in patients having gastrointestinal symptoms. In every subject there was fecal blood loss ranging from 0.2 to 13.5 ml. per day.

The manner by which salicylates influence bleeding is not known. The theory of hypersensitivity has been postulated[23]. It was endorsed by Dixon, but admittedly could not account for the majority of the cases.

Hyperacidity has been attributed to aspirin and could explain the activation in chronic ulcers. The occult blood found in one case of pernicious anemia reported by Alvarez and Summerskill[10], however, could not substantiate this hypothesis.

It is generally accepted that adrenal corticosteroids may produce peptic ulceration. The stimulation of the adrenal cortex by salicylates has been demonstrated[24] and could contribute to the hemorrhagic tendency in known peptic ulcer.

Hypoprothrombinemia following large doses of salicylates in man has been suggested as being responsible for the bleeding in certain cases[25,26]. Other observers, however, have failed to confirm either prolonged prothrombin time or alteration in bleeding and clotting time in those cases employing mild to moderate doses[10]. In our series, all prothrombin determinations reported were within normal range.

Frick[27] noted that salicylates increased capillary fragility and permeability. In his cases he was able to demonstrate this with positive Rumple-Leeds tests in patients on salicylates; the test returning to normal when the drug was withdrawn. This theory appeals to us as a likely answer and bears further investigation.

The clinical observation of epitaxis[28], posttonsillectomy[29,30] and vaginal bleeding[31] after salicylates would infer a systemic effect on blood coagulation.

TABLE VII

SYMPTOM FOR WHICH SALICYLATES WERE TAKEN

Headache	13	41%
Abdominal pain	6	19%
Arthritis	5	16%
Nervousness	3	9%
Bursitis	2	6%

In a great number of those succumbing to salicylate poisoning, it was especially noted that the hemorrhages were petechial and ecchymotic[2]. The presence of albuminuria with red and white cell casts during the treatment of rheumatoid arthritis lends further evidence of the effect on capillary structures[2].

Quick[32], whose name is synonomous with factors of hemostasis, stated speculatively that first in importance is the integrity of the vessel wall. Even in hyperheparemia, hemostasis is remarkably effective and breaks down only when the injury to the capillaries is severe.

Salicylate intake is greatest in emotionally and physically taxed individuals. In our series headaches, pain, and nervousness contributed 91 per cent of the reasons for taking salicylates.

The equation can now be simplified. Stress plus salicylates equal capillary engorgement plus increased capillary fragility equals hemorrhage.

COMMENT

There remains little doubt that salicylate administration influences hemorrhage from the gastrointestinal tract. The exact mechanism is not known, but

the appearance of bleeding from various organs, namely nose, genitourinary tract[33], uterus—independent of the gastrointestinal tract—suggests that this is due to systemic effects, not local. This apparently varies with individuals, not on a hypersensitivity basis, but probably on a basis of increased capillary fragility and the nonspecific effects of stress. Repeated observations have failed to confirm a prothrombin deficiency.

It is our opinion, therefore, that prolonged salicylate analgesics should not be used in the presence of ulcer, active or inactive. Furthermore, the surgeon should be ever mindful of the possibility that this drug could be responsible for massive upper gastrointestinal hemorrhage. The failure to find a definite bleeding site in chronic aspirin users should reinforce the probability that the drug is responsible. And, following a subtotal gastrectomy in these cases, care should be taken to withhold further salicylates postoperatively.

Summary

1. Stress of different types including physical and emotional trauma and infection is the primary cause for gastric erosions and may well be the sole cause for the incidence of hemorrhage of the gastrointestinal tract.

2. Salicylates have been shown to account for occult gastrointestinal bleeding both clinically and experimentally. It has been suggested that the effect is upon increasing capillary fragility.

3. In the presence of stress, salicylates may be responsible for a reasonable percentage of massive gastrointestinal hemorrhages, cause undetermined, as well as hemorrhage from activation of known gastrointestinal pathology.

4. Forty-six per cent of the cases of massive gastrointestinal hemorrhages at Touro Infirmary from 1 July 1959 to 1 January 1960 had taken salicylates within 24 hours prior to admission to the hospital.

5. Laboratory investigations are in progress to study the relationship between salicylates and capillary permeability.

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Discussion

Dr. John M. McMahon (Bessemer, Ala.):—I should like to compliment both of the authors on their papers. Since Dr. Schloss has devoted a portion of his remarks and Dr. Kaplan's paper deals *in toto* with review of the possible—and I use "possible" in quotation marks—effects of salicylates on the gastrointestinal tract I should like to discuss these papers together. I have been interested in this problem for some 10 years during which period I have been active in the teaching program in rheumatic diseases at the University of Alabama Medical Center in Birmingham.

Probably many of you in the audience are aware that a considerable number of rheumatologists feel that aspirin does not cause gastrointestinal hemorrhage. At our 1959 meeting in Los Angeles, however, I was most impressed with the exhibit of Muir from England dealing with the local erosive effect of aspirin and its role in bleeding. Dr. Howard Holley, Chief of Rheumatic Diseases at the University of Alabama, was not particularly impressed by this evidence; however, in February of 1960 I visited with Dr. Walter Bauer and his group at Massachusetts General Hospital in Boston. At that time Dr. Marion Ropes stated that in her many years of practice in rheumatology she had only seen about 3 patients with rheumatoid arthritis who had been gastrointestinal bleeders. These had been on large doses of aspirin for extended periods. In the April, 1960 issue of the *British Medical Journal* an article from one of the Rheumatic Disease Units appeared which stated that aspirin does not cause ulcer or anemia. The authors pointed out that many of their cases instead of bleeding had an increase in the amount of hemoglobin as the disease improved.

Looking at this from the other side of the fence, however, in our own practice about 50 per cent of the patients presenting with bleeding ulcer gave a history of taking aspirin or some salicylate previously. This is roughly what Dr. Kaplan found. Whether a *post hoc, ergo propter hoc* type of reasoning is applicable here is difficult to say.

Many patients who take aspirin regularly complain of constipation. In our rheumatoid arthritics about ½ who are on large doses of aspirin for many months had no gastrointestinal complaints. About ⅛ will get heart burn after a period of several weeks. This can usually be alleviated by switching to a buffered aspirin. I have, however, only seen 1 or 2 patients with rheumatoid arthritis who had massive bleeding after taking aspirin for many months and in whom I felt the aspirin was responsible for the bleeding.

As you know the problem of anemia is very common in patients with rheumatoid arthritis. It seldom responds to iron. We have done exhaustive studies on some of our rheumatoids who had a hemoglobin of around 50 per cent and were not able to indicate that they were losing blood. I think perhaps that this problem can be resolved by some work which appeared in the 26 May 1960 issue of the *New England Journal of Medicine* entitled "The Chemical Basis of the Buffered Acetylsalicylic Acid Controversy". The authors point out that the solubility and dissolution rate of various types of aspirin vary greatly. Some are very soluble; others quite insoluble and the authors could correlate the incidence of bleeding with the insoluble types of preparation.

In support of this argument I have noted that some patients could take either aspirin or Robaxin, a widely used muscle relaxant, separately without trouble; however, as soon as those patients were switched to a new combination marketed as Robaxisal, the drug was noted to produce nausea quite promptly. If one looks at this preparation it is a very hard slick tablet which I am sure

is quite insoluble. Consequently, physical characteristics of a preparation may be equally as important as its chemical characteristics.

One comment about Butazolidin: About 9 or 10 years ago when the drug was first introduced we encountered numerous side-effects. In the last 8 years or so, however, very few patients have complained of heart burn and none in our practice have developed peptic ulcer provided the dosage does not exceed 400 mg. a day and the preparation taken after meals or with some food such as milk. Occasionally in patients with a history of previous ulcer or heart burn we use the alka form.

The comments about Thorazine I think are well taken. The psychiatrists in our area, however, still feel that this is a drug of choice in the treatment of *delirium tremens*. I don't, however, feel that we see as much of the DT's complicating severe cirrhosis in our area as one sees in the north.

A last comment—several months ago we saw a patient who developed a large gastric ulcer about 1 week after being started on Benadryl for the treatment of Parkinsonism. The ulcer healed completely after a program of medical treatment. The Benadryl was later on resumed without difficulty. This shows some of the difficulties involved in again using a *post hoc, ergo propter hoc* type of argument.

Dr. H. B. Eisenstadt (Port Arthur, Texas):—I would like to ask Dr. Kaplan if he has made a study on the intake of salicylates of the patients who come into his hospital and who do not have any stomach disorder. The use of salicylate drugs is so widespread that there might be no statistically significant difference between the two groups. Dr. McMahon speaks of patients who take salicylates in large quantities for the treatment of rheumatoid arthritis and do not show any increased number of gastric lesions. Just as patients with rheumatoid arthritis react differently to ACTH and cortisone administration than other persons, it is conceivable that people with peptic ulcer diathesis react in a different way to salicylates than persons without tendency to ulcer formation.

Dr. Eugene M. Schloss (Philadelphia, Pa.):—I would like to make one brief remark if there's time.

This controversy about salicylates, in many aspects, is a controversy between the gastroenterologist and the rheumatologist. I suggest just one point: as the individual with rheumatic fever or rheumatoid arthritis often exhibits a capacity to take immense quantities of aspirin or other salicylates without apparent untoward effects, it may well be that these patients are able to exhibit greater gastric tolerance for the drug, whether this be mediated via capillary permeability, capillary sensitivity or other yet unknown mechanism.

Certainly, we in the field of gastroenterology are accustomed to seeing a considerable amount of hemorrhage which is apparently the result of the ad-

ministration of aspirin or other salicylates, whereas this frequency has not been encountered by the rheumatologist.

Dr. Murrel H. Kaplan (New Orleans, La.):—There is little question but that clinical observations and interpretations can be disputed. The experimental work of the caliber of Matsumoto and Grossman as well as Dixon and his group, however, both of whom employed CR^{51} in recovering fecal blood loss must be accepted.

Among the rheumatologists, Bargar and Douthie expressed the thought that aspirin could not be incriminated as a cause of anemia in the chronic arthritics. Dixon and his group in the very next issue of the *British Medical Journal* refuted this by recalling their work with CR^{51}.

The answer to the question of the incidence of bleeding from salicylates in the average individual can best be approached by referring to the control studies of Stubbe and Matsumoto and Grossman. In the final analysis, it is my feeling that the data of the latter investigators should leave little room for any other conclusion than that salicylates do influence fecal blood loss.

IPRONIAZID JAUNDICE*

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Although iproniazid was first used in the treatment of tuberculosis, it is now chiefly used as a psychic energizer. Its use, however, is on the wane because of its propensity for liver damage. The mode of action is unknown. The tendency, albeit small, to produce severe liver necrosis has sharply limited its use. It has, however, been used for years in innumerable cases without any difficulty. When jaundice does develop it is usually devastating. The diagnosis presents many problems, but with care, reasonable accuracy is possible. Inasmuch as a definite diagnosis is difficult to make, many cases of viral hepatitis have been called iproniazid jaundice. There is no strong differential feature.

Mode of Action

The mechanism of action is an unknown quantity. Iproniazid is a hydrazine, and as shown by the work of Bodansky in 1924[1], this family contains potent hepatotoxic agents. There has since then been an accumulating volume of work done with these subtances in animals[2-5] using chemical variations of the hydrazine base. Most of these produce fatty livers in animals, some being far more toxic than others. In all experiments, a high dosage was employed compared with that currently used in humans. The manner in which iproniazid blocks metabolic pathways is yet to be learned. It can definitely lower the ammonium level in patients with liver disease, but has no action on the ammonium metabolism of the liver[6].

In animals this compound can reduce monoamine oxidase activity almost completely[2]. Similar substances such as Marplan, Catron, Nardil and Niamid also are inherently capable of attacking the liver, but to a much lesser degree[7-9] Nardil and Niamid are now being increasingly more used, and effectively. A good evaluation should soon be possible. Both Catron[2] and Marplan[10] are more active in the brain in smaller doses than iproniazid, and hence can be used with less threat to the liver. The value of this differential feature, however, is yet to be proven.

Usage

The drug has been given to tuberculosis patients since 1952 and found effective[11-13]. Because of its toxicity, however, it was discontinued in a few years. Nevertheless, it is to be noted that most of these toxic effects involved other

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areas, and it was not because of its menace to the liver that it was stopped[12,13]. Inasmuch as the tuberculous patient always had an uplift in mood on this drug, it was natural to shift to psychiatry, where it was indeed found to be a potent drug[14]. It is from its usage in this capacity that the jaundice cases are mainly coming. And yet this it not a consistent feature. In fact, of over one hundred thousand cases, only a very few result in hepatitis[15]. The incidence has been placed at 1:4000[16].

Toxicity

There has been a large and extensive experience with the drug. But only in the past few years have reports of severe jaundice been coming. In the earlier case studies, jaundice was little if any problem. Indeed, some patients developing abnormal liver function tests on iproniazid, returned to normal while still taking the drug[11,17]. In other cases, with abnormal function tests prior to the drug, no liver disease developed during iproniazid treatment[18,19]. Again, liver function tests have become abnormal[20] on iproniazid with return to normal after omitting this drug, but no untoward effects on restarting.

As it slowly became evident that iproniazid could produce liver damage of a serious degree[21-25], much more careful attention was paid to this aspect of the drug. The accumulating data pointed to a drug capable of causing severe hepatocellular damage. Carefully planned studies began to appear[18,19,26]. Attention was aimed at discovering a test that could reliably give warning that trouble was brewing. Although transaminase has been put forward as such[26] there are far too many cases where the test has not proven to warrant this role[17,18,27]. At present, it would seem advisable to employ any routine screening profile, such as bromsulfalein, thymol turbidity, cephalin flocculation, transaminase, serum bilirubin, urine urobilinogen. Unfortunately, as of the moment no known barrage of tests currently available has been of help in determining those who will develop jaundice. Careful studies[18,19] including liver biopsies[19], at the start and during treatment, have as yet failed to reveal a test or tests capable of differentiating the safe from the unsafe. Nevertheless, patients under treatment with this drug should advisably be followed with function tests. It is from this testing and retesting that we may yet see a trustworthy diagnostic barrage.

Comparative Features and Pathology

In our early experience with this jaundice, it was natural to equate it with previously known common drug "hypersensitivity" reactions affecting the liver, notably chlorpromazine and testosterone. These latter drugs and iproniazid are similar in their lack of relationship to dosage, time of onset, and predictability. But it soon became apparent that whereas the latter two drugs were cholestatic, iproniazid jaundice was unequivocally hepatocellular. Also whereas treatment of these cholestatic agents is often little more than omitting the drug and applying

routine symptomatic measures, the hepatitis of iproniazid frequently requires vigorous therapy. The pathological picture of the cholestatic family has been well presented[16,18,29]. The pathological picture of iproniazid hepatitis has also been well presented[16,22,23]. There is necrosis of varying degrees, usually extensive. This process may involve the central portion, or all of the lobule. Infiltration by mononuclear cells is a constant feature. This cannot be differentiated from that of viral hepatitis.

Diagnosis

The clinical picture is equally difficult to differentiate from viral hepatitis. In some recent excellent presentations[19,30,31] the clinical picture is reviewed. The similarity to that of viral hepatitis is close enough to be indistinguishable. In fact, the similarity is so marked that the entity of iproniazid jaundice is clouded. There can be little doubt, however, that this entity does exist. The causal relationship of the drug to this type of hepatitis seems well established. Kahn and Perez[31] and Felix, Schwartz and Rifkin[30] have attempted to put this on a definite basis. There is little doubt as to this diagnosis, and the growing literature on the subject attests to its common acceptance. Where it can be definitely ascertained in these cases that there has been no exposure to the virus of hepatitis or to other drugs, in the presence of iproniazid treatment, the diagnosis seems clear. Actually, there is no unequivocally positive diagnosis; this is assumed with the occurrence of a viral hepatitis-like picture after the ingestion of iproniazid where no other cause for jaundice exists. Indeed, if the patient were seen without the knowledge of this drug being taken, a diagnosis of viral hepatitis would be made without hesitation. Nevertheless, from the composite experience, certain criteria seem established. The diagnosis may be reasonably made if:

1. an hepatocellular hepatitis develops during treatment with iproniazid,

2. it is clinically, chemically, and pathologically similar to, or identical with, the picture of viral hepatitis,

3. absence of exposure

   a. to sources of infectious hepatitis,

   b. to parenteral medication, or if such medication is given, rigid sterile technic used,

   c. to other hepatotoxic drugs.

4. no preexisting liver disease of this type.

Because of the long action time of the monoamine oxidase inhibitors after being omitted, jaundice may occasionally occur after the drug is stopped, per-

haps up to a week or more[27]. In general, then, the diagnosis depends on the presence of a hepatocellular disease after iproniazid, where no other factors are operative. Where there has been exposure to viral hepatitis, or other hepatotoxic drugs, the decision will indeed be difficult, and occasionally impossible to make. As a clinical aid, Kahn and Perez[31] have pointed to the frequent absence of fever in this type of hepatitis. This may well be a deciding factor. Be it as it may, there can be little doubt that some cases reported as iproniazid jaundice were actually viral hepatitis, and that this may well also occur in the future. Application of these criteria, however, will be helpful in the differentiation.

Anicteric Stage

With the unpredictable variations and fluctuations of the liver function tests, it is difficult to diagnose those patients with anicteric hepatitis with any degree of certainty. To date, this problem has not been an issue. All available data and literature have properly been concerned with the full blown picture itself, its treatment, and methods of selecting those susceptible. But with a better understanding of the more typical picture, the atypical patterns are becoming increasingly more important. This diagnosis obviously would be made in those instances of iproniazid hepatitis without jaundice. With our present knowledge, however, this presents great difficulties. Changes in liver function tests alone are not sufficient evidence. Liver biopsy would be needed. Recognition of the anicteric stage will be helpful in filling in the gaps in our knowledge. It may also be of benefit in helping determine those tests best able to select the susceptibles.

Treatment

Treatment differs little from that of viral hepatitis. The value of steroids is difficult to assess[31]. In the reported cases some have improved with them and some without them. The reverse also seems true. There is no specific therapy. Regardless of treatment, once jaundice sets in, the mortality may reach 20 per cent[16].

Chronicity

As to the future picture, the probability of cirrhosis is not known. At the moment, the problem is most easily approached by comparison with viral hepatitis. Because of the marked similarity between these diseases, it would follow that the complications would be similar. Hence, we may reasonably expect to see postnecrotic cirrhosis after sufficient time has elapsed, and should be on the lookout for this. This type of cirrhosis occurs in a very small percentage of viral hepatitis[32]. Iproniazid jaundice is far less common than viral hepatitis; hence a far lesser incidence of cirrhosis can be expected. Popper[27] in discussing the pathology mentions tendency to transition into postnecrotic cirrhosis. There has been insufficient time to establish this entity. But even with the fragments of

data now available, it seems clear that we may expect to see this form of cirrhosis in the future as a sequel of iproniazid hepatitis, albeit infrequently.

Status of Iproniazid

Iproniazid has been employed in many and varying capacities: tuberculosis[12], mental depression[14], angina pectoris[33], hypertension[34], rheumatoid arthritis[20], and a similar monoamine oxidase inhibitor, niamid, has been found strongly beneficial in asthma[35]. Its toxicity as confirmed by the studies of liver involvement[27], and other areas[12] limit its use. Nevertheless, it has proven its worth. A vast accumulated experience with iproniazid going back over most of the past decade cannot be lightly discarded. There is a very definite place for this drug in the medical armamentarium.

Summary

Iproniazid hepatitis appears to be a well established entity, closely resembling viral hepatitis. Of the various avenues available, clinical, chemical, pathological, a clear cut differential cannot be made. Some criteria have been advanced that may be helpful in this respect. In those cases where iproniazid has been given and a viral hepatitis-like picture develops, the diagnosis should be considered.

The mechanism of action is not known, but the possibility appears to be due to its hydrazine fraction. This may act through its role as a monoamine oxidase inhibitor.

The recognition of the anicteric stage is becoming important. This will be helpful in a better understanding of its mode of action, its true incidence, and in assessing the severity of the disease.

Cirrhosis has not yet played a part in the picture. From the available data, however, we may expect to see some form of cirrhosis occurring in the future.

Despite its toxicity, carefully used, there is a definite place for iproniazid among present day medications.

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Discussion

Dr. Stanley S. Sidenberg (Cleveland, Ohio):—Dr. Milner's paper has been very thorough and yet I am sure that he would be the first to admit that he has failed to exhaust the truth of the subject.

From a small personal experience and in perusing the voluminous literature built up in a relatively brief time on iproniazid poisoning I think these points are worthy of reflecting upon.

Experimentally investigators find it almost impossible to poison livers with iproniazid. Three strains of mice are completely resistant. One strain, an AKR strain is on the other hand extremely susceptible to iproniazid poisoning.

Iproniazid hepatitis in humans cannot be correlated as Dr. Milner said with dosage levels nor with duration of medication.

Cerebral disease apparently has more than a coincidental relationship with liver malfunction. We see it in Wilson's hepatolenticular degeneration, in hepatic coma, and strikingly in the disproportionate number of viral hepatitides that end up with severe mental depressions in the psychiatrists' hands.

Bowman of Mayo's has already theorized that iproniazid may be more hepatotoxic in the absence of certain hepatic enzymes concerned with iproniazid degradation; and isopropyl hydrazine, an intermediate breakdown product of iproniazid degradation, is known to be particularly toxic to liver sinusoids and to the reticuloendothelial system.

Iproniazid as was mentioned is basically a hydrazide akin to the old acetylphenylhydrazine that we used in polycythemia. The toxic element in the iproniazid is supposed to be, as I understand it, a double NH group and the rest of the moiety merely determines organ affinity and therefore directs damage to the liver or blood or to peripheral nerves as the case may be.

Liver toxicity estimates in the literature run from a high of one and four tenths per cent of all cases down to one in 500,000 cases, depending on the observer.

What may this mean?

First that hidden genetic liver enzyme defects may render a small number of people especially susceptible to iproniazid.

Second that iproniazid may break the barriers of a contained viral hepatitis pool and permit rampant spread. Popper has talked about that.

Third that further modifications of the iproniazid moiety may direct its action away from the liver and hence the search for variations.

Fourth and last, in view of the frequent presence of overt or latent liver diseases in depressions it is well to recall an old maxim. Do not use a club to swat a fly. Having taken the precaution to examine the liver and having obtained a liver profile it might be wise to still use some of the milder energizers such as Tofranil or Permitil for anxiety states while reserving the more potent iproniazid for the severe depression.

THE RESPONSE OF THE GASTROINTESTINAL TRACT TO INJURY*

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and

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Physiological studies of the injured and of patients undergoing the trauma of elective operations have demonstrated that the systemic response to injury is a response of every organ and presumably every cell in the body. In general, the response of the gastrointestinal tract tends toward hypofunction or altered function in the postinjury period.

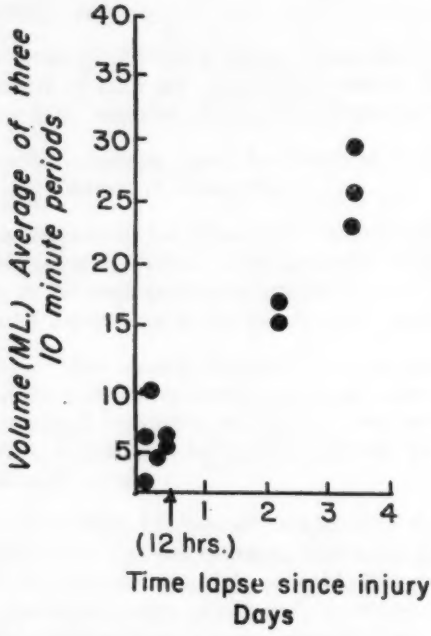

Fig. 1—Volume of salivary secretion in six men with major injuries and shock.

The response of the gastrointestinal tract in the human may be conveniently studied by investigation of the known function of that organ in question. In

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most instances this means a measure of volume of secretion, or change in motility or absorption patterns under injury of various magnitudes. The biochemical assay of hepatic function has been broadly applied to this problem.

Study of the volume of salivary gland secretion following minor to severe injury[17] demonstrated a decrease in volume of saliva immediately after severe injury but not after minor injury (Fig. 1). In those patients with severe injury in whom a marked reduction of salivary flow was demonstrated, surgical shock had been present.

Instances of esophageal or gastroduodenal ulceration and perforation are well recognized following thermal burns[4,29]. Friesen[9], citing the Jefferson study of extensively burned patients in which there was a 3.8 per cent incidence of gastrointestinal tract ulcers, noted an increase in gastrointestinal mucosal con-

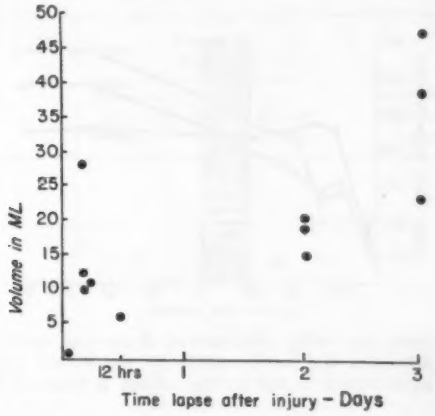

Fig. 2—Volume of gastric secretion in six battle casualties with major injuries.

gestion in burned animals. Weigel and his associates[36] reviewed 139 patients who had gastrointestinal ulceration complicating burns. Of 10 patients who had severe hemorrhage, the ulcer was located in the duodenum in 9 patients and in the stomach and duodenum in 1. Of 7 patients with perforation, 5 had multiple perforations involving the esophagus, stomach and duodenum. We have seen the esophagus perforate within a few hours after a massive thermal burn of a child.

Gastric function following injury is marked by alterations in the volume and acidity of gastric secretion[17] (Fig. 2). In battle casualties suffering minor injuries, volume and acidity were found to be within normal limits. In the severely injured, however, volume decreased and each severely injured patient who was studied was found to have achlorhydria. Following resuscitation and operation, volume and acid concentration were found to return to normal limits

(Table I). Studies by Drye[7] and Gray[12] demonstrate conflicting data on the effect on gastric secretion of adrenal gland stimulation.

The absorptive function of the gastrointestinal tract was studied utilizing absorption of deuterium oxide[6,18,22] (Fig. 3). The equilibration curve reflects the effects of peristaltic activity, gastrointestinal absorption, the state of intravascular circulation and diffusion through body fluids. In patients burned to a moderate extent, deuterium oxide absorption is impaired but remains more rapid than after abdominal injury. In instances of abdominal injury, deuterium oxide absorption is markedly delayed for several days. Studies of gastrointestinal motility following operation have demonstrated that intestinal motility is usually present almost immediately following major abdominal operations[26]. This early activity cannot be correlated closely with the presence of bowel sounds. Clinical experience has demonstrated well that motility is markedly depressed. The presence

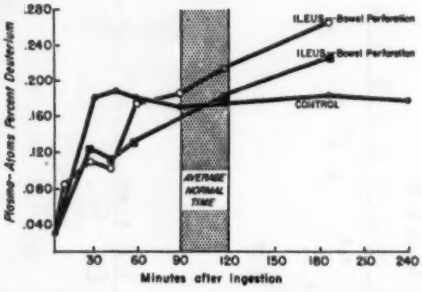

Fig. 3—Equilibration curves for orally administered deuterium oxide. In the two patients with ileus, equilibration was not complete by the second postinjury day in either patient, while equilibration in the normal subject is achieved in 90 to 120 minutes after ingestion.

of a limited motile function, however, suggests that absorption following abdominal injury is dependent at least in part on the state of the circulation (absorptive capacity) rather than on motility. The volume secretion of small bowel in postoperative patients with long intestinal tubes in place shows initially a decreased volume of secretion following major intraabdominal surgery[15]. It is of interest that in the recovery phase, motility recovers before absorption so that frequently, the initial bowel movements are watery.

Hepatic function in the injured man has been rather intensively studied[1,3,10,32]. Plasma bilirubin was found to be normal in the unresuscitated casualty for the first 3 to 5 hours after injury. Following transfusion, a variable pattern emerged (Fig. 4). The pattern of bilirubin response was more closely correlated with the occurrence of shock and the location of the wound and later the presence of a wound hematoma, than with the amount of blood received or the magnitude of injury. An elevation of serum bilirubin concentration to 2.0

to 4.0 mg. per cent during transfusion and operation, however, were frequently, even characteristically, found on the day of combat injury. A second rise in bilirubin concentration often followed about the fifth day. Urobilinogen excretion in the urine paralleled the serum bilirubin levels with increments on the day of injury and on the 4th or 5th days afterwards. Bromsulfalein retention was usually elevated on the first postoperative day. The presence of shock or an abdominal wound was usually associated with the most marked retention. Occasionally the 45-minute retention was as high as 30-40 per cent. Plasma prothrombin activity was depressed to 50 per cent of normal following wounding and resuscitation with stored blood. After the fourth day, a second depression occurred. These depressions could not be prevented by the administration of Vitamin K. Cephalin flocculation was characteristically abnormal prior to resuscitation. Following transfusion and operation, the cephalin flocculation remained 2 plus to 4 plus for several days. Fibrinogen synthesis and glucose formation appeared essentially normal.

TABLE I

VALUES FOR FREE AND TOTAL ACID IN GASTRIC JUICE IN 6 CASUALTIES WITH MAJOR INJURIES

Patient	Free acid (degrees)		Total acid (degrees)	
	Immediately following injury	2-3 days after injury	Immediately following injury	2-3 days after injury
1. Multiple soft tissue wounds	0	21	12	25
2. Multiple soft tissue wounds	0	36	11	32
3. Wound of thigh moderate shock	0	7	26	43
4. Perforation lung, liver, gallbladder	0	32	34	72
5. Perforation chest	0	—	9	27
6. Perforation colon	0	—	—	—

Gallbladder function was studied by oral and intravenous cholecystography[19]. In traumatized battle casualties with wounds in any region, the gallbladder was not visualized but with very few exceptions. Of the 5 patients whose gallbladders were visualized roentgenographically during the first few days after injury, none had experienced an intraabdominal injury (Table II). Utilizing the Cholografin technic, Sparkman[33] has demonstrated that the gallbladder can be

clearly defined after nonspecific injury. Rousselot et al[30] were unable to visualize the gallbladder, utilizing oral technics for as long as a month following perforation of a peptic ulcer or appendix. Gullick[13] gave his patients Telepaque prior to elective operation. Serial x-rays demonstrated continued visualization of the gallbladder postoperatively until the patients resumed oral intake. Thereafter the gallbladder emptied and visualization ceased.

Pancreatic function may be assessed indirectly by evaluation of the plasma amylase[20]. In instances of abdominal injury in the region of the pancreas, serum amylase activity increases markedly (Fig. 5), whereas in abdominal injuries distant to the pancreas, plasma amylase activity falls below normal levels. In elective surgical operations in the region of the pancreas, results from our laboratory suggest a similar trend. The administration of cortisone has no demonstrable effect on the serum amylase level. After major extraperitoneal operations, uptake of I^{131}-labelled triolein is decreased significantly; no change in oleic acid

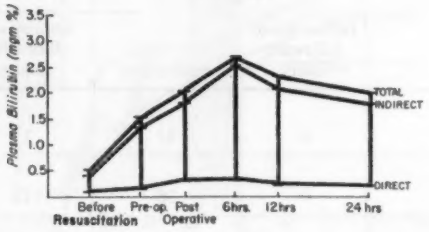

Fig. 4—The effect on serum bilirubin of resuscitation with stored blood—24 severely injured men.

absorption is noted[11]. This further suggests that pancreatic suppression may be an instrinsic part of the general suppression of gastrointestinal function following trauma.

Comment

By 1929, Cannon had arrived at a unitarian concept of the general response of the animal to strong emotional states and pain. He wrote, "If the secretion of adrenin (adrenalin) is increased in strong emotional states and in pain, that constitutes a fact of considerable significance, for, as already mentioned, adrenin is capable of producing many of the bodily changes which are characteristically manifested in emotional and painful experiences"[2]. His researches over the years had demonstrated that pain, injury and strong emotional states are attended by many of the same gastrointestinal responses noted above. In order to document hypersecretion of adrenalin, Cannon resorted to several methods of bioassay which were cumbersome and laborious. It remained for others to demonstrate changes in catechol amine metabolism in response to injury.

In 1942, Elmes and Jefferson[8] reported their studies of the effect of various forms of anesthesia on the epinephrine content of the adrenal glands. Under the conditions of their study, 2.7 to 6.7 per cent decreases in content of epinephrine were noted per hour. Increases in plasma epinephrine levels during various stages of anesthesia were reported by Watts[35]. The experience of the research team in Korea was hampered by the lack of a method that would yield reproducible results in the measurement of catechol amine levels in the injured. Since then, wider experience with biochemical analysis of norepinephrine and epinephrine has been gained and several studies of the differential changes of these substances with anesthesia and operation have become available[14,16,23,28].

TABLE II

Results of Cholecystographic Studies in the Severely Injured Battle Casualty*

Number with injury	Average time post-injury—hours	Drug	Route	Number with	
				Visualization	Nonvisualization
1—Normal	—	Iodeikon	Oral	1	—
1—Normal	—	Iodeikon	Intravenous	1	
2—Normal	—	Priodax	Oral	1	
2—Normal	—	Telepaque	Oral	2	
11	4.0	Iodeikon	Intravenous	2	10
13**	3.3	Iodeikon	Oral	0	13
13	4.8	Telepaque	Oral	3	10

*There were no instances of direct injury to bowel.
**Included one patient with penetrating wound of the liver and one patient with acute appendicitis.

Uniformly, injury, represented by surgical operation, is attended by measurable increases in plasma levels of the catechol amines. Thus Hardy[15], Hume and Bell[24] and others have extended Cannon's original observations on the increases in adrenal vein blood of catechol amines under a variety of circumstances.

Since the widespread response of the gastrointestinal tract occurs at a time when the tide of catechol amines is at its height (during anesthesia, during and following operation and in burns), as well as when adrenocortical response is at its maximum, the effect of exogenous cortisone on specific gastrointestinal functions was studied[25]. Cephalin cholesterol flocculation, serum amylase activity and oral cholecystography were studied in normal individuals receiving 200 mg. of cortisone daily. The previously described alterations in these specific func-

tions of the gastrointestinal tract in the battle casualty could not be reproduced by administration of cortisone. Related studies in the experimental animal and in man have offered no consistent pattern of response of portions of the gastrointestinal tract to corticoids. Gray[12] noted reversal of the achlorhydria of Addison's disease with corticoid stimulation, while Dragstedt[5] noted no consistent response to corticoid stimulation in Heidenhain pouch dogs. Sandweiss[31] noted increase in survival time in Mann-Williamson dogs over the controls when ACTH was administered. Others[27,39] have documented gastric hypersecretion with corticoid administration but no consistent causal relationship between exogenous corticoid administrations and the etiology of peptic ulceration has been established. These conflicting views have recently been summarized by Wiederanders[37].

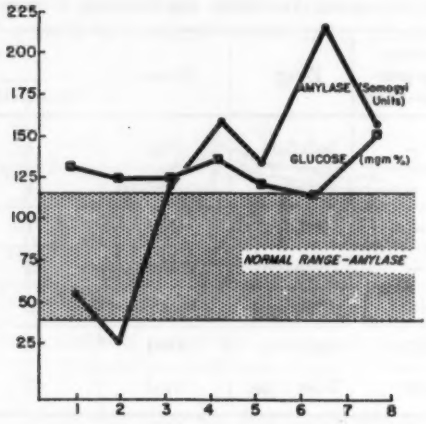

Fig. 5—Serial serum amylase and blood glucose determinations in a severely injured man with indirect (abdominal wound) injury to the pancreas. Days following injury is plotted along the abscissa.

The search for a mechanism of disordered gastrointestinal function with injury continues on these and other fronts. One of the most pressing problems in surgical care today is the prevention of paralytic ileus. Studies of electrolyte changes in the injured as well as in the elective surgical patient have indicated disorders in calcium and phosphorus metabolism[21,34,38]. Currently, correlations with disordered gastrointestinal function are not possible but newer knowledge of the general response to injury may give further direction to such studies.

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Discussion

Dr. Murrel H. Kaplan (New Orleans, La.):—This paper is very thought-provoking. I'm not really prepared to discuss this paper intelligently for several reasons. First, it takes one schooled in physiology, biochemistry and pathology; secondly, it assumes that one has had extensive experience in human investigation, which admittedly I haven't; and last, but not least, I unfortunately didn't have the opportunity to speak with Dr. Howard prior to hearing his paper this morning.

As a clinician, however, I've made several observations relative to stress in gastrointestinal disease. Of particular interest has been the hypothesis that any stress, be it physical, such as injury, or emotional, such as rage, can be responsible for the precipitation or the exacerbation of pancreatitis.

The reason for this seems very simple and yet logical.

(Slide) This is a picture or graphic drawing of the response of the body to rage, but this could be any stress—the response is mediated through two systems, namely, the hypothalamopituitary adrenal axis and the hypothalamo-autonomic nervous system.

Two different stressors do not necessarily give identically the same nonspecific responses, but these two systems are the two systems that are involved.

(Slide) The pancreas is an anlage of the upper gut—this you are all most familiar with—(Slide) and has the same nerve and blood supply.

It does not, therefore, seem to be too far fetched to assume that this organ should escape the nonspecific effects of stress which is known to provoke disease in the stomach and duodenum.

On the contrary, the anatomical differences leave me with a strong feeling that pancreatitis occurs more frequently. Time does not permit us to go into the subject of autoimmune mechanism in pancreatic disease. I'm sure all of us enjoyed this paper immensely. Timidly, I bow out with a confession that as a clinician I can only make a report of my observations, while an investigator and scientist, Dr. Howard, gives you facts.

FURTHER EVALUATION OF SPLENIC PULP MANOMETRY AS A DIFFERENTIAL DIAGNOSTIC TEST OF ACUTE UPPER GASTROINTESTINAL BLEEDING*

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The management of severe bleeding from esophagogastric varices differs appreciably from and is more demanding of the physician than bleeding from other sites in the upper alimentary tract (peptic ulcer, neoplasm, erosive gastritis, and esophagitis). It is therefore important to promptly recognize which of the lesions mentioned is causing the hemorrhage. A diagnostic dilemma most often arises in the patient with historical or physical evidence of cirrhosis of the liver. Patients with bleeding varices secondary to an extrahepatic portal bed block are also occasionally seen. Limitations of conventional methods of differential diagnosis (gastrointestinal x-rays, trial balloon tamponade, esophagoscopy, liver function tests) are well recognized.

In most cases of bleeding esophagogastric varices, there is associated portal hypertension. Several investigators have demonstrated that pressure within the splenic pulp accurately reflects the portal venous pressure[1,2,3]. In similar studies by us the highest levels of portal tension have been seen in patients who were bleeding or had bled from varices[4]. We have found that splenic pulp manometry performed under emergency conditions, i.e., during periods of gastrointestinal bleeding is a relatively safe and simple procedure[5]. We believe that the immediate recognition of the presence or absence of portal hypertension in a given patient who is bleeding from the upper alimentary tract should be of distinct help in determining whether that patient may or may not be bleeding from varices.

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TABLE I

ELECTIVE SPLENIC PULP PRESSURES OF PATIENTS WHO HAD BLED FROM ESOPHAGOGASTRIC VARICES

Patient	Age	Sex	Splenic pulp pressure (mm. of water)	Patient	Age	Sex	Splenic pulp pressure (mm. of water)
H.Y.	74	M	150	H.W.	52	M	400
M.M.	43	M	275	J.D.	42	F	400
J.J.	50	M	277	M.N.	50	F	401
A.M.	62	F	280	R.C.	35	M	406
F.L.	68	M	282	J.T.	59	M	410
K.S.	58	M	285	E.P.	23	M	415
V.R.	51	M	293	W.F.	59	M	415
W.B.	62	M	300	E.R.	45	M	416
E.R.	33	F	300	L.L.	56	M	420
C.S.	59	M	306	J.G.	44	M	423
T.M.	48	M	313	J.M.	70	M	425
C.E.	46	M	325	C.A.	40	F	429
M.D.	40	F	326	S.M.	58	M	433
R.C.	45	M	340	E.T.	58	M	433
C.K.	9	M	350	B.F.	60	F	437
E.T.	55	M	353	A.G.	5	M	450
M.F.	45	F	356	M.P.	45	M	450
W.E.	52	M	357	B.C.	56	M	460
J.C.	53	M	358	R.I.	43	M	465
F.T.	44	M	363	K.T.	46	M	465
G.R.	32	M	367	A.C.	48	F	465
M.C.	42	M	370	V.R.	51	M	468
M.M.	44	M	371	L.K.	34	F	470
C.B.	57	M	375	J.H.	32	M	472
B.P.	52	M	377	S.F.	57	F	475
B.G.	62	F	380	N.P.	51	F	480
M.M.	41	F	383	A.J.	28	F	485
B.J.	29	F	383	A.K.	46	M	530
J.M.	52	M	383	J.S.	43	M	540
P.W.	62	F	388	A.F.	61	F	550
F.S.	4	M	390	M.C.	72	F	580
L.C.	42	M	395	J.L.	62	F	600
M.F.	57	M	395	M.O.	51	M	600
E.R.	46	M	395	V.T.	47	F	600
H.B.	54	F	400	Z.B.	16	F	650
L.D.	62	F	400				

Mean pressure = 406.5 mm. of water

TABLE II

ELECTIVE SPLENIC PULP PRESSURES OF PATIENTS BLEEDING FROM SITES OTHER THAN VARICES

Patient	Age	Sex	Splenic pulp pressure (mm. of water)	Source of bleeding
T.B.	31	M	70	Duodenal ulcer
E.B.	64	M	73	Erosive gastritis
C.W.	57	M	80	Duodenal ulcer
P.G.	53	M	93	Duodenal ulcer
D.J.	36	F	105	Duodenal ulcer
Y.K.	46	F	105	Duodenal ulcer
E.C.	61	M	113	Duodenal ulcer
W.E.	57	M	131	Duodenal ulcer
G.S.	64	M	140	Carcinoma of stomach
E.S.	53	M	140	Duodenal ulcer
W.A.	30	M	145	Hiatus hernia, esophagitis (cirrhosis)
J.A.	41	M	147	Marginal ulcer
C.R.	56	M	147	Gastric ulcer
G.S.	63	M	150	Duodenal ulcer
M.F.	42	F	150	Hemoptysis—pulmonary tuberculosis
S.S.	63	M	157	Leiomyosarcoma of stomach
E.C.	35	M	157	Gastritis (cirrhosis)
J.D.	47	M	165	Hiatus hernia, esophagitis
M.R.	65	M	165	Erosive gastritis
M.B.	57	M	165	Gastritis
T.F.	68	M	170	Hiatus hernia, esophagitis
H.K.	38	F	173	Gastritis
F.A.	43	M	180	Gastritis
C.D.	31	M	180	Duodenal ulcer (cirrhosis)
E.C.	41	M	180	Duodenal ulcer
J.S.	39	M	190	Duodenal ulcer
F.S.	44	M	190	Erosive gastritis
J.M.	27	M	193	Erosive gastritis
L.F.	50	M	195	Gastric and duodenal ulcers
W.R.	33	M	195	Erosive gastritis
T.T.	39	M	200	Duodenal ulcer
G.C.	59	M	200	Carcinoma of stomach
J.S.	45	M	203	Erosive gastritis

Mean pressure = 178.0 mm. of water

TABLE II *(continued)*

ELECTIVE SPLENIC PULP PRESSURES OF PATIENTS BLEEDING FROM SITES OTHER THAN VARICES

Patient	Age	Sex	Splenic pulp pressure (mm. of water)	Source of bleeding
A.S.	58	M	215	Duodenal ulcer
J.O.	40	M	219	Gastritis (cirrhosis)
C.B.	43	M	220	Duodenal ulcer
O.D.	77	F	225	Erosive gastritis
J.J.	66	M	230	Carcinoma of stomach
D.M.	62	M	232	Gastric ulcer
M.C.	61	M	253	Duodenal ulcer, esophagitis (cirrhosis)
D.H.	55	M	258	Erosive gastritis
M.B.	72	M	273	Duodenal ulcer
W.S.	45	F	275	Gastric ulcer
M.C.	65	M	280	Carcinoma of stomach
M.H.	65	M	288	Cancer of the esophagus

Mean pressure = 178.0 mm. of water

Our preliminary report of splenic pulp manometry as an emergency test in the differential diagnosis of the site of acute upper gastrointestinal hemorrhage listed our results in a limited number of cases[5]. It is the purpose of this paper to present our extended experience with this procedure.

MATERIALS AND METHODS

Commencing in January, 1957, the splenic pulp pressures of 165 patients who had recently bled or were actively bleeding from the upper gastrointestinal tract were recorded. Forty-nine of the 165 manometric readings were obtained as the initial discriminatory test during an acute bleeding episode. The remaining 116 readings were carried out electively some time after bleeding had ceased. Verification of the diagnosis was subsequently established in each instance. Diagnosis of portal hypertension and varices, of course, was further substantiated by portography. Additionally, other roentgenographic as well as surgical or postmortem evidence was used in confirming the diagnosis.

Details of the technic of combined splenic pulp manometry and portography are reported in an earlier paper[6]. An abridgement of the technic of splenic pulp manometry is herein presented. Pressures were determined by inserting a No. 18 gauge spinal needle into the spleen. Local anesthesia was routinely used in the adult. The usual site of needle insertion was the left ninth intercostal space in

the posterior axillary line. This site varied depending on the habitus of the patient and the size of the spleen. The patient is instructed to breathe easily and then holds the breath during actual insertion of the needle. Although transit of the needle through the spleen could often be felt, this was not constant. The needle was inserted 1 to 3 cm. into the splenic pulp, depending on the degree of splenomegaly. A constant drip of blood from the needle hub usually confirmed the intrasplenic location of its point. The needle was subsequently attached to a water manometer with its zero point at table level. A short length

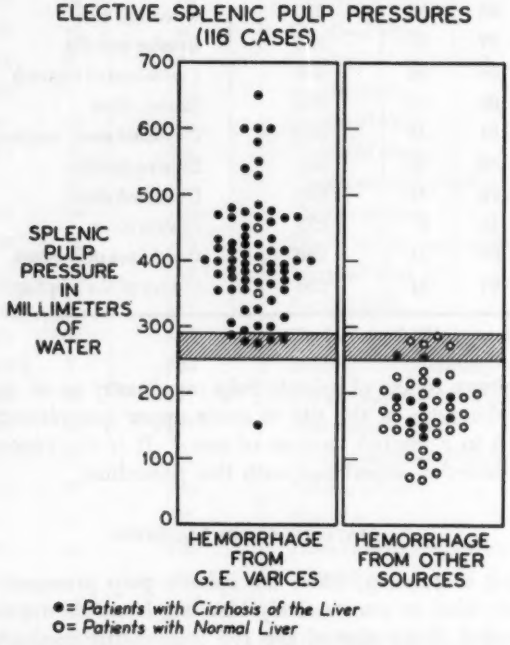

Fig. 1—Graph showing distribution of splenic pulp pressures of 116 patients according to the source of upper gastrointestinal bleeding. Pressures were recorded electively after bleeding had ceased.

of plastic veno-tubing interposed between the needle and the manometer prevented a rigid system and minimized the possibility of splenic laceration during subsequent respiratory motions. Since the needle may on occasion become plugged with a thrombus, routine needle clearing with 1 or 2 ml. of normal saline was utilized to avoid errors in mensuration. We have adopted the average of three sequential readings as representative of the splenic pulp pressure. The corrected baseline for transposition to portal pressure was taken as 12 cm. above the plane of the table on which the patient was lying supine. This represents

the average figure of our measurements in 52 adult cadavers and indicates the distance from the table to the anterior surface of the second lumbar vertebra, which has also been the correction point in determining actual portal pressure in patients at operation.

Most of the splenic pulp pressures taken on a nonemergency basis were performed on the x-ray table and were immediately followed by splenoportography. Many of the emergency pressures were taken while the patient was in bed or on a stretcher.

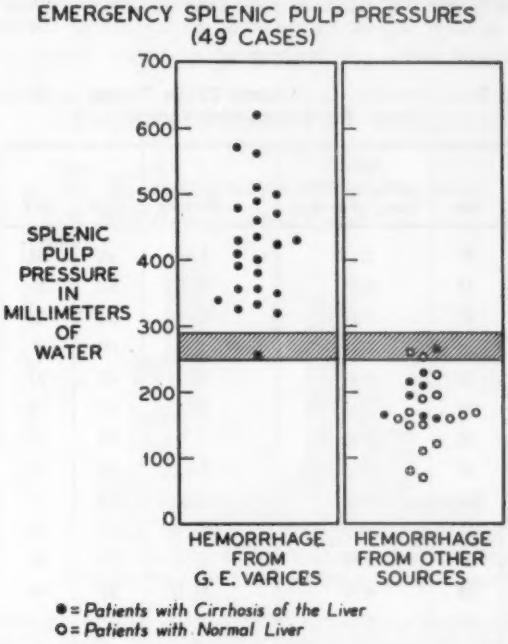

Fig. 2—Graph showing distribution of splenic pulp pressures of 49 patients according to the source of upper gastrointestinal hemorrhage. Pressures were recorded during active bleeding.

Results

Routine diagnostic data obtained subsequent to elective manometry confirmed our provisional opinion of the presence of esophagogastric varices as the site of bleeding in 71 patients. The remaining 45 patients bled from other lesions. The great majority of these 116 patients had a presumptive diagnosis of cirrhosis of the liver. Varices were the site of bleeding in 24 of the 49 patients in whom splenic pulp manometry was performed as the initial differential diagnostic test during an acute bleeding episode. Whether performed as an elective procedure

or under emergency conditions, splenic pulp pressures of patients who had bled from varices were consistently higher than those of patients who had bled from other sites (Tables I, II, III, IV, and Figures 1 and 2). The mean pressure taken electively in patients who had bled from varices was 406.5 mm. of water. The mean pressure obtained under emergency conditions in patients bleeding from varices was 424.4 mm. of water. The mean pressure of patients bleeding from other sites in the upper gastrointestinal tract was 178.0 mm. of water under nonemergency conditions, and 176.4 mm. of water under emergency conditions. All patients both in the elective and emergency series whose pressures were above 290 mm. of water had bled or were bleeding from varices. On the other

TABLE III

EMERGENCY SPLENIC PULP PRESSURES OF PATIENTS TAKEN DURING AN EPISODE OF BLEEDING FROM ESOPHAGOGASTRIC VARICES

Patient	Age	Sex	Splenic pulp pressure (mm. of water)	Patient	Age	Sex	Splenic pulp pressure (mm. of water)
H.C.	54	F	257	J.M.	46	M	430
W.B.	45	M	320	N.H.	53	F	430
A.R.	56	F	327	C.M.	54	M	435
P.M.	61	M	333	B.C.	69	F	460
R.C.	45	M	340	R.H.	47	M	470
H.W.	52	M	351	J.C.	57	M	480
R.M.	43	M	356	T.K.	34	F	490
E.C.	46	M	358	J.K.	42	M	500
J.M.	44	M	380	E.K.	45	F	510
L.D.	58	F	390	G.M.	62	M	560
L.D.	72	M	400	L.H.	58	M	570
J.D.	33	M	410	M.D.	37	M	620
F.M.	49	M	423				

Mean pressure = 424.4 mm. of water

hand, with one exception, all patients whose pressures were below 250 mm. of water had bled or were bleeding from a lesion other than varices.

Thus there remained a zone of overlap which included patients bleeding from esophagogastric varices as well as patients bleeding from other lesions. This area of fallibility was surprisingly narrow and delimited, ranging from 250 mm. to 290 mm. of water. Eleven (9 per cent) of the elective pressures and 4 (8 per cent) of the emergency pressures fell into this zone. In these patients, the findings of serial splenoportography were ultimately essential in determining the presence or absence of varices.

Taken collectively, 93 per cent of all patients bleeding from varices had pressures over 290 mm. of water. Many (54 per cent) had pressures of 400 or more mm. of water. Frequency distribution of splenic pulp pressures taken both electively and under emergency conditions was similar (Figs. 3 and 4).

Comment

Our earlier experience with the use of splenic pulp manometry as an emergency test in the differential diagnosis of upper gastrointestinal bleeding proved singularly safe and accurate and prompted us to pursue its use almost routinely. We have continued to realize an accuracy of 90 per cent in determining the presence or absence of varices in patients during active hemorrhage.

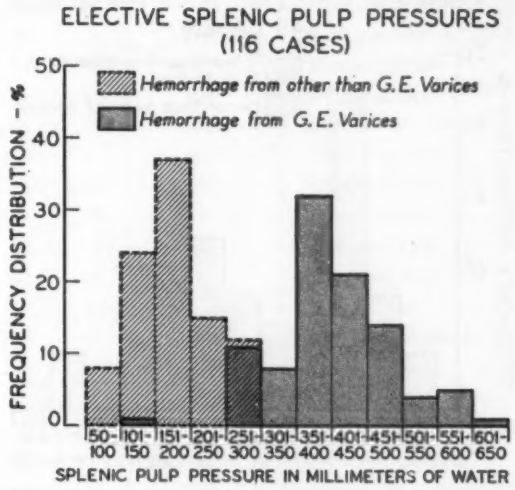

Fig. 3—Graph showing frequency distribution of splenic pulp pressures of 116 patients according to the source of upper gastrointestinal hemorrhage. Pressures were recorded electively after bleeding had ceased.

Several objections and possible limitations of the usefulness of the procedure were anticipated when we first used this test. Probably the most obvious of these was the possibility of the concomitant presence of varices and peptic ulcer. The demonstration of an elevated portal pressure in a patient bleeding from the upper gastrointestinal tract does not, of course, absolutely rule out the possibility of bleeding from a site other than esophageal varices. In fact, we believe that if emergency ligation of varices is indicated for control of varical hemorrhage, the abdominal approach, as Welch has advocated[7], is preferable because of the possibility of a concomitant peptic ulcer or other lesion in the upper abdomen. Our experience, however, seems to indicate that when portal hypertension is

present the most probable site of bleeding is varices. On the other hand, a normal portal pressure, with rare exception, rules out the possibility of massive bleeding from varices and the necessity for balloon tamponade or consideration of emergency portacaval shunt or ligation of varices. During the course of this study we have encountered two patients with x-ray evidence of both active peptic ulceration and esophagogastric varices. Splenic pulp pressure was elevated in these patients. Fortunately, these patients stopped bleeding spontaneously with the use of conservative measures. It was not possible to determine from which lesion bleeding had occurred.

Experimental work in animals has indicated that portal pressure does not necessarily parallel changes in arterial pressure. Wiggers, Opdyke and Johnson

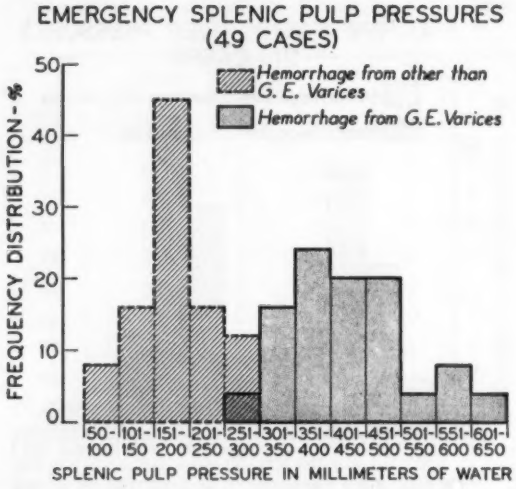

Fig. 4—Graph showing frequency distribution of splenic pulp pressures of 49 patients acording to source of upper gastrointestinal hemorrhage. Pressures were recorded during active bleeding.

have shown that in dogs, portal pressure after a temporary decline tended to return to or toward control values during a period of hypotension secondary to bleeding[8]. These physiological observations in animals initially suggested to us that portal hypertension in the human likewise might not be modified even when varical hemorrhage resulted in hypovolemia and arterial hypotension. Our clinical observations of markedly elevated portal pressures in 12 human subjects bleeding massively from varices and with low systolic arterial pressures tend to support this concept.

A definitive diagnosis of the presence or absence of esophagogastric varices cannot be made in those acutely bleeding patients whose splenic pulp pressures

fall in the area of ambiguity between 250 and 290 mm. of water (in which varices may or may not be present). In our experience, uncontrollable hemorrhage in patients whose splenic pulp pressure has been within this range has

TABLE IV

EMERGENCY SPLENIC PULP PRESSURES OF PATIENTS TAKEN DURING AN EPISODE OF BLEEDING FROM SITES OTHER THAN ESOPHAGOGASTRIC VARICES

Patient	Age	Sex	Splenic pulp pressure (mm. of water)	Source of bleeding
J.O.	69	M	70	Duodenal ulcer
F.K.	63	M	80	Hiatus hernia, esophagitis
H.S.	39	M	110	Telangiectasia of small bowel
T.M.	63	M	121	Erosive gastritis
H.C.	49	M	150	Duodenal ulcer
J.M.	49	M	150	Gastritis
H.N.	56	F	160	Erosive gastritis
F.A.	31	M	160	Duodenal ulcer
R.L.	64	M	160	Duodenal ulcer
T.B.	53	M	162	Duodenal ulcer
R.H.	62	M	170	Duodenal ulcer
R.T.	54	F	166	Gastric ulcer
R.H.	45	F	165	Duodenal ulcer
P.T.	30	F	170	Gastritis
J.R.	57	M	190	Diverticulitis
L.T.	50	M	195	Gastric and duodenal ulcer
A.B.	48	F	195	Erosive gastritis
F.M.	43	M	210	Hiatus hernia, esophagitis
G.B.	68	M	215	Erosive gastritis
D.R.	68	M	228	Cancer of cardia of stomach
P.T.	46	M	230	Erosive gastritis, postportacaval shunt
A.M.	41	M	252	Duodenal ulcer
R.E.	55	M	260	10 months postportacaval shunt, erosive gastritis
F.W.	60	F	265	Duodenal ulcer

Mean pressure = 176.4 mm. of water

always originated from a peptic ulcer. Conversely, uncontrollable hemorrhage from varices has always been associated with a definitely elevated pressure. There were 11 such instances of uncontrollable hemorrhage from varices. The

splenic pulp pressures of these patients ranged from 358 to 620 mm. of water with a mean pressure of 463.3 mm. of water. Splenic pulp manometry is therefore clinically useful even in the area of fallibility.

The patient (Fig. 1) in whom an elective splenic pulp pressure of 150 mm. of water was obtained promptly stopped bleeding from varices after admission to the hospital. Varices were not suspected until portography was performed. The occurrence of bleeding varices associated with normal portal tension is rare and therefore does not appear to limit the procedure.

The safety of the procedure is reflected in the minimal morbidity reported in large series of splenic portography[6]. Splenic puncture for the purpose of manometry alone should have even lower morbidity. We have experienced no complications with splenic pulp manometry. Emergency puncture of the spleen could not be achieved in only 3 instances. Severe blood coagulation defects or inability of the patient to cooperate are contraindications to the procedure.

Perhaps the greatest dilemma in the differential diagnosis of acute upper gastrointestinal hemorrhage arises in those patients with some historical or physical stigma of cirrhosis. Many of these patients may be spared the risks and discomfort of an unnecessary balloon tamponade[9] if splenic pulp pressure is first tried to establish the presence or absence of portal hypertension.

The procedure is a relatively simple one, requiring no complex apparatus or laboratory technic. For this reason it may be easily utilized in the small as well as the large hospital during hours in which facilities or personnel might not be available for the prompt performance of either complex roentgen examinations such as splenic portography or of emergency liver function studies. In larger clinics manometry may serve to limit portography to those patients with elevated pressures.

Summary

A previous report by our group indicated that emergency splenic pulp manometry was 90 per cent accurate in determining the presence or absence of esophagogastric varices in patients actively bleeding from the upper gastrointestinal tract. An extended clinical experience is herein reported and confirms the preliminary report. The immediate determination of the presence or absence of varices gained by the emergency use of splenic pulp manometry has continued to result in a more accurate appraisal and more effective management of these patients. The use of the procedure has become routine on the surgical and medical services of St. Vincent's Hospital, especially in those patients with historical or physical evidence suggesting cirrhosis of the liver.

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Discussion

Dr. Samuel Levine (Philadelphia, Pa.):—It is always indeed a pleasure to listen to an authority and a pioneer in any subject and in this case, of course, too, and I have enjoyed this presentation very much.

Dr. Rousselot and his group were one of the foremost and preeminent authorities on this subject and one of the pioneers in this country.

It is interesting that splenoportography was done as early as 1949 at Johns Hopkins. I believe by Dr. Blalock, Dr. Bahnson and Dr. Sloan.

Now as to the matter of increased splenic pressure particularly indicated, as Dr. Rousselot has said, in patients who on the one hand come in and who bleed and you don't know the diagnosis. On the other hand the patient has had a history of bleeding and is not bleeding at a moment of admission. We personally prefer to do a gastrointestinal study to determine whether or not there are any esophageal varices.

One has to remember again, as Dr. Rousselot has said, that there are certain cases where the splenic pressure is normal. It's also of interest—we have had experience as others have had where a patient may have an increased splenic pressure due to portal hypertension. A year may elapse and the patient may be re-examined without any operation, without any operative shunt and occasionally nature produces shunts with a drop of the splenic pressure.

In instances of normal splenic pressure with esophageal varices and bleeding the question comes up, why the hemorrhage?

It suggests that there are other factors besides portal hypertension producing hemorrhage such as ulcerative factor or possibly esophageal varices without any marked increase in the general circulation.

I think it would be of interest for someone to correlate the study of increased splenic pressure versus the incidence of varices in the portal circulation. In other words, to plot the splenic pressure against the splenography—the splenography, of course, would show where the collaterals are present, and in certain instances I would think that there are marked esophageal varices through the short gastric veins where the general increased pressures may not attain.

Jaundice is a contraindication in our judgment to splenography or increased splenic, or during splenic pressure. Again if a patient has ascites it may be a good idea to tap the abdomen prior to doing a splenic puncture.

Occasionally, again, one may be disturbed by the needle being too close to the splenic artery, in which case you may get a false notion as to what the splenic pressure may be.

Again, I think one has to remember that what the patient does may affect splenic pressure. If the patient coughs, if the patient is apprehensive and contracts his muscles, the respirations are increased; that again may produce an inaccuracy in splenic pressure. In other words, you have to have a cooperative patient.

Occasionally we have had difficulty in combining splenography with increased splenic—with doing the splenic pressure because leaving the needle in the spleen for any length of time may loosen up the needle and you may get a subcapsular injection.

Dr. Louis M. Rousselot (New York, N. Y.):—I think Dr. Levine has made several very pertinent observations.

We would like to again mention this problem of varices and normal portal tension often referred to by some. We showed one such observation in that first graph of 116 consecutive cases. If you noticed, in the entire 116 consecutive observations in the group, there was only one case representing an incidence of less than one per cent who had a normal pressure, but who subsequently was proven to have varices.

Furthermore, the question is raised of how often will a person with portal hypertension and varices show a reversal of the process over a period of time. I think there has been ample evidence to show that in certain cases of acute toxic liver injury, particularly in the hepatitides with only moderate degree of cirrhosis, some of these people can have transient portal hypertension and varices with subsequent subsidence of the process under medical care, and lowering of portal tension.

Our group has shown that in carbontetrachloride-induced liver damage in rats, in which varices and portal hypertension were produced experimentally; varices disappeared in a few of the animals in which the hepatotoxic agent was discontinued.

The frequency of such a reversal, if it occurs in humans, is very limited.

As Dr. Levine mentioned, quoting Sherlock, and our group has independently made the same observations, there is a linear correlation between the appearance of varices and other collaterals including large natural portasystemic shunts and portal hypertension.

The discussor likewise mentioned, contraindications to the use of this procedure, referring especially to uncooperative and agitated patients. In this I concur.

INTEGRATED CONTROL OF PLASMA PROTEIN LEVELS AND LIVER SIZE*

ANDRE D. GLINOS, M.D.

Washington, D.C.

The maintenance of plasma protein levels within physiological limits is considered to involve variable rates of synthesis and catabolism regulated by the plasma protein level itself. As a consequence, and since with the exception of gammaglobulin, serum proteins are almost exclusively of hepatic origin, any decrease in their circulating blood levels would be expected to induce an increased outflow from the liver. This increased outflow is attributed to increased plasma protein synthesis in the individual liver cells. It is, however, obvious that increased outflow of plasma protein from the liver could also occur as a result of an increase in the number of hepatic cells. Recent experimental evidence indicates that this latter mechanism is actually operating and that as a consequence control of plasma protein levels and control of liver size are linked. The evidence was obtained by submitting to experimental verification three obvious consequences of this concept.

The first consequence is that plasma protein depletion should cause the liver to grow. This possibility was investigated by submitting adult male albino rats to plasmapheresis, the classical experimental treatment for depleting plasma protein[1]. In essence, the treatment consisted in periodic bleedings of these animals followed by reinjection of the blood cells, after separating them from the plasma, in saline suspension having a volume equal to the volume of the blood withdrawn. In order to exclude interference from stress, control rats were treated in an identical way but in this case the bleedings were followed by reinjection of the whole blood. It was found that whereas in such control rats the incidence of dividing cells in the liver remained at the low level characteristic of the continuous physiological replacement of cells lost through wear and tear, the incidence of mitosis in the treated rats increased as a function of the intensity and duration of the treatment. In rats treated for 4 days at a high rate of plasmapheresis the incidence of dividing cells in the liver was increased by a factor of 100. Thus, it was demonstrated that experimental acute plasma protein depletion is followed by a process of active growth in the liver[2,3].

The second consequence of the notion that control of plasma protein levels and liver size are related is that experimental increase of the plasma protein concentration in animals the liver of which is growing, should have an inhibitory effect on the growing liver. This possibility was investigated by increasing the plasma protein concentration, through fluid intake restriction, in rats undergoing

*Read before the 25th Annual Convention of the American College of Gastroenterology, Philadelphia, Pa., 24, 25, 26 October 1960.

liver regeneration after partial hepatectomy. In essence, the treatment consisted in withdrawing drinking water from rats submitted to partial hepatectomy and tube-fed a liquid diet containing only 3 per cent water. Control rats were submitted to the same treatment but allowed drinking water *ad libitum*. The total duration of the experiment was 64 hours and total body water loss in the treated animals was below 10 per cent, in agreement with the finding that no appreciable metabolic disturbances occur in the rat after 3 days of water intake restriction[4]. It was found that the incidence of dividing cells in the liver of the treated animals was by 80 per cent lower than in the controls. Thus, it was demonstrated that experimental increase of the plasma protein concentration effectively inhibits the growth of the liver[3,5].

The third consequence of the notion that the mechanisms controlling liver size and plasma protein levels are related is that pathological conditions characterized by hypoproteinemia and hypoalbuminemia would be expected to stimulate liver growth. This possibility was investigated by inflicting a third degree burn involving 30 per cent of the total body surface on partially hepatectomized rats and comparing the rate of growth of their liver with that of similarly hepatectomized normal controls. To avoid nutritional interference both experimental and control rats were tube-fed an identical isocaloric diet. It was found that at 48 hours after the operation total serum protein and albumin were lower in the burned than in the control animals by 13 and 44 per cent respectively. The weight of the residual liver, and total liver protein nitrogen were higher in the burned than in the control animals by 10 and 14 per cent respectively. Statistical analysis showed this difference to be highly significant. Thus, it was demonstrated that pathological conditions characterized by hypoproteinemia and hypoalbuminemia stimulate the growth of the liver[6]. The fact that the particular condition investigated was burn adds to the significance of this finding since it is known that in burned animals growth during the healing of tissues other than liver is inhibited[7], and that such animals have a negative nitrogen balance of their carcass protein[8].

The results of the three experiments discussed indicate that the amount of extracellular plasma protein synthesized by the individual liver cell per unit time is related within certain limits to the amount of the extracellular protein present by a constant ratio. Lowering of the level of the extracellular plasma protein beyond a certain limit results not only in increase of plasma protein synthesis but also in activation of intracellular protein synthesis and eventually cell division. As a result of the increased number of liver cells producing extracellular protein the lowered level of plasma protein is restored to normal. Thus, the level of extracellular plasma protein appears to control the rate of synthesis of intracellular protein and ultimately the total number of cells and the size of the liver, the plasma protein level itself depending on the number of liver cells present.

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Discussion

Dr. Joseph Gambescia (Philadelphia, Pa.):—Thank you for the privilege of appearing before you this morning and reviewing this fine paper on a fascinating subject.

The ability of the liver in an organism to replace destroyed or dying parenchymal cells is well recognized. That this marvelous compulsion to restore functioning cellular mass is under some type of homeostatic control can be surmised although the factors involved in the call to regenerate or replace are presently shrouded in a nebulous ignorance.

It can also be surmised that under situations of increased demand it is conceivable that the liver can respond within limits to this demand by increasing the efficiency of the existing parenchymal cells and/or increasing the number of functioning cells.

Dr. Glinos has postulated that part of the mechanism controlling hepatocellular growth and/or replacement is the level of serum protein. This is an inviting, as well as an interesting postulate and as with all good works more questions have been raised than have been answered.

It is the duty of a discusser to ferret out some of the questions and hence possibly stimulate further thought and investigation.

Consequently I would like to ask Dr. Glinos the following questions.

First, since plasmapheresis removes, in addition to serum protein, other plasma constituents, how can we assume that plasma protein depletion alone was responsible for the reported changes?

Secondly, since the number of mitotic figures seen under normal conditions is interpretable as a reflection of the normal cellular loss and certainly this is true in partial hepatectomy, why is not an increase in mitotic figures interpreted

as increased loss rather than interpreting this increase in mitotic figures as evidence of growth or increase in cellular mass?

And thirdly, do you believe in the light of your experiments that the administration of human salt-poor albumin is contraindicated in individuals with hypoproteinemia, especially those with decompensated liver disease, since an increase in the level of circulating protein may actually inhibit cellular growth and thus slow the very thing we are trying to quicken, namely, the replacement of dead or dying hepatic cells?

Dr. Andre D. Glinos (Washington, D. C.):—The experiments in plasmapheresis alone considered by themselves do not, of course, prove that it is the plasma protein which is responsible for the induced growth. I believe that our concept is at the present time supported by those three pieces of evidence which all seem to be linking the serum protein with the activation of the liver cells and their eventual cell division, but I don't think that if you take the plasmapheresis experiments by themselves they will prove this relationship. This is the reason why we proceeded to do the experiments on the two other points I talked about.

The second question, I am not sure I understand. I believe you said that since the small number of mitotic figures seen in the intact normal animal is interpreted as a result of the normal cellular loss, the increase in mitotic figures obtained by plasmapheresis could also be interpreted as due to increased loss of cells, instead of considering it as evidence for growth alone. This would assume that when we plasmapherese the animal there is death of liver cells. We have examined this possibility carefully, and there doesn't seem to be any cellular death following plasmapheresis; neither does there seem to be any cellular death in the burned animals. I think that the experiment with the burned animal is very significant because other metabolic studies which were conducted by Dr. Levenson and his group at Walter Reed have shown that wound healing in other tissues, for example, the skin is delayed and the over all nitrogen balance in the burnt animal is negative. Nevertheless, the liver does show an increased growth and I think that this is quite significant with respect to the operation of this specific mechanism of liver growth which involves the serum protein.

With respect to the last comment, this is a clinical problem, and I don't think I'm qualified to answer; I haven't done any clinical work for 15 years and the problems are very complex there. I would like to discuss it with Dr. Gambescia and other clinicians to see what conclusions could be drawn.

PANCREATIC FUNCTION IN PORTAL CIRRHOSIS*

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Ever since animal experimentation revealed that ligation of the pancreatic ducts produces fatty liver there has been increasing interest in the relationship between pancreatic pathology and liver disease[1,2]. Loss of external pancreatic secretions and resultant decrease in the absorption of amino acids (methionine) was presumed to be the etiologic factor behind the production of fatty liver[3,4]. Other authors have reported the high incidence of portal cirrhosis, including ascites, in patients with pancreaticolithiasis[5,6] and more recently some have given priority to pancreatic fibrosis as the pathologic precursor of portal cirrhosis and its sequela[7]. The latter reports are concerned with the results of autopsy data. On the other hand, Stinson, Baggenstoss and Morlock have reported on pancreatic pathology in 75 patients with portal cirrhosis[8]. The degree of severe fibrosis, interstitial inflammation and ductal and acinar dilatation was considerably higher in cirrhotics than in controls. There was, however, no evidence of significant pancreatic functional impairment in their patients with cirrhosis.

Gross, Comfort, Wollaeger and Power investigated the steatorrhea that often occurs in primary hepatic parenchymatous disease[9]. In their report the total values for volume, bicarbonate and enzyme concentration in pancreatic exocrine secretion were normal or greater than normal in the patients with liver disease. After secretin the mean volume in their group of patients was further increased; there appeared to be hypersecretion rather than hyposecretion. Dreiling and Hollander reported normal pancreatic function studies following secretin stimulation in patients with hepatitis[10].

The present study was undertaken to determine the exocrine pancreatic secretion in patients with portal cirrhosis following secretin* stimulation. The characteristics of the normal secretin response and the significance of this response as a test for pancreatic disease have been thoroughly investigated[11,12].

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*We are indebted to Eli Lilly & Co. and Dr. J. B. Hammond of the Clinical Research Division for the generous and consistent supply of the secretin used in this study.

Method and Material

Twenty-five patients from the wards and the hepatology clinic of Bergen Pines County Hospital, Paramus, N. J. are the subjects of this study. All presented evidence of portal (alcoholic or nutritional) cirrhosis, clinically, and by laboratory means confirmed by biopsy and/or autopsy.

All subjects were examined after a 12-hour fast. A double-lumened gastroduodenal (Diamond) tube was positioned under fluoroscopic control with the proximal openings in the stomach and the distal in the 2nd and 3rd portions of the duodenum with the tip proximal to the ligament of Treitz. The position

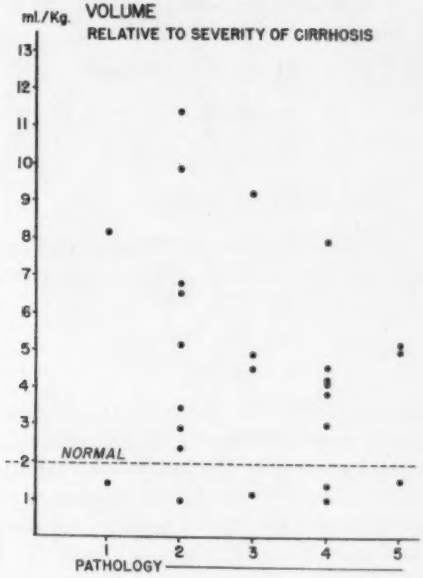

Fig. 1

of the tube was also visualized after the completion of the procedure. Both series of outlets in the tube were under simultaneous constant suction of 120 mm. mercury with an electric pump. After a preliminary run of approximately 5 minutes and/or until the duodenal secretions became alkaline, a basal secretion was aspirated for 20 minutes. Then a secretin dose of 1.0 clinical unit per kg. of body weight was administered intravenously. A 60-minute postsecretin aspiration was then collected consisting of three 20-minute periods. The studies performed on the gastric specimens were volume and pH and on the duodenal specimens, volume, pH, bicarbonate concentration and amylase. The pH was

determined with a Beckman glass electrode, bicarbonate concentration by a modified Van Slyke method and amylase according to a modified Somogyi (Lagerlof). Duodenal specimens with a pH lower than 6 were discarded.

The normal values for exocrine pancreatic secretion following secretin have been determined by a statistical study of data in normal patients[13]. Minimal normal values have been established as, total volume 2.0 ml./kg., bicarbonate concentration 90 mEq./l and total amylase secretion 6.0 Somogyi units/kg. In 3 patients the test was performed twice at different admissions. No reactions were encountered following the intravenous administration of secretin. In 4 patients the pancreas was examined at necropsy.

Classification of liver pathology was listed as:

Grade I: Early portal cirrhosis
" II: Moderately advanced
" III: Advanced
" IV: Far advanced
" V: Florid cirrhosis

The classification of liver pathology was based upon the amount of fat, fibrosis, nodularity, bile, hyalin and necrosis in the biopsy specimens. These modalities were categorized as 1-4 in intensity.

Results

A volume less than 2 ml./kg. was present in 6 patients (Fig. 1). Of these, one was early (Grade I) with considerably fatty change, one was moderately advanced (Grade II), one advanced (Grade III), two far advanced (Grade IV) and one florid cirrhosis (Grade V). On the other hand, a volume of more than 6 ml./kg. (3 x the normal) was obtained in 7 patients. Of these, one was Grade I, two were Grade II and one Grade III and one Grade IV. A bicarbonate concentration of less than 90 mEq./l as the maximal figure was found in 16 patients (Fig. 2). In this group there were three patients in Grade I, four patients in Grade II, two patients in Grade III, four in Grade IV and three patients in Grade V. The amylase determinations were less than 6 Somogyi units/kg. in 13 patients as follows: two in Grade I, three in Grade II, three in Grade III, four in Grade IV and one in Grade V (Fig. 3).

Comment

No consistent parallelism was found in this series between the concentration of exocrine pancreatic secretion as obtained following secretin stimulation and the degree or severity of liver disease.

The most sensitive index of pancreatic deficiency was bicarbonate concentration. The average bicarbonate concentration in this series was 71 mEq./l. Nevertheless, only 16 of the 25 patients presented maximal bicarbonate concentrations of less than 90 mEq./l. A survey of the scatter data reveals for example that in Case 24 with a profoundly depressed bicarbonate concentration of 29 mEq./l the pathology was only Grade II or moderately advanced portal cirrhosis. On the other hand, other patients presenting a more severe form of liver disease, Grade IV or Grade V, possessed higher values of bicarbonate concentrations and in some instances above the minimal normal figure of 90 mEq./l. In general, although variable, there appeared to be more correlation

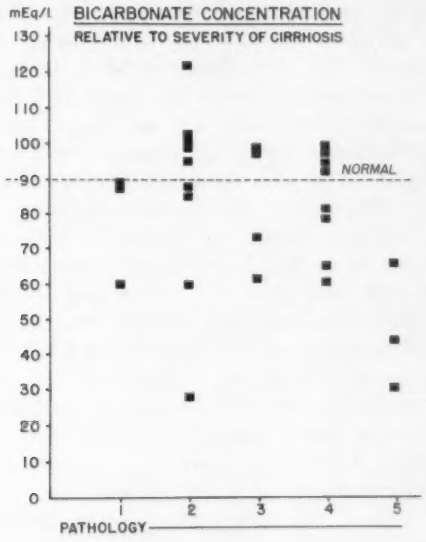

Fig. 2

between the degree of pathology and the reduction in bicarbonate concentration than any other modality.

Closely approaching the incidence of abnormality in bicarbonate concentration was exocrine amylase expressed in Somogyi units. In 13 patients the results were below the normal of 6 units/kg. The correlation between the severity of the pathologic process and the degree of depression of amylase excretion was more inconstant. For example, in Case 5 with a severely depressed amylase level of 2.7 units/kg., the pathologic process was represented as being Grade I or mild with considerable fatty metamorphosis. On the other hand, in Case 22 with a pathologic process classified as Grade V or florid cirrhosis, the amylase determination was 10.5 units/kg. far above the minimum of 6 units/kg. Volume

depression appeared to be the least sensitive finding and in only 6 patients was the volume in ml./kg. below the minimal normal figure of 2 ml./kg.

The results of the pancreatic function tests reveal that a depression in one modality, for example in bicarbonate concentration, was associated with a depression in either amylase or volume in more than 70 per cent of the patients. The association of depressed functional values was found to exist most frequently between bicarbonate and amylase. Simultaneous depression of volume, bicarbonate and amylase was present in only 3 patients.

In 4 patients we were able to study the pancreas. The disassociation of function to pathology is well illustrated in three of the patients who came to autopsy. In 2 patients in whom there was significant depression of volume, bicarbonate and/or amylase, the pancreas was reported as negative. One of these patients (Case 4) who died during an episode of massive esophageal bleeding had two previous admissions. On her first admission with hepatic decompensation, jaundice, ascites, etc., the liver biopsy was read as Grade III cirrhosis and there was depression of all pancreatic functional studies—volume, bicarbonate and amylase. The most severe abnormality was in amylase concentration, 2.8 Somogyi units/kg. At her second admission, one year later, the pathology report of the liver biopsy was Grade IV cirrhosis. At this time pancreatic function studies other than amylase were within normal limits and the latter was improved (4.8 Somogyi units). At her final admission death occurred within four hours from hemorrhage and a secretin test could not be performed. At necropsy the liver pathology was again noted as Grade IV but the pancreas was reported as showing "no significant abnormality". In a second patient (Case 12) with a similar report of no pancreatic pathology abnormalities in pancreatic function were severe depression of amylase to 1.9 units/kg. and bicarbonate of 61 mEq./l. The liver pathology was reported as Grade IV cirrhosis. In the two other patients, however, the pancreas presented more significant pathology. In Case 7 the pathologic report included severe intraductal plugging by amorphous secretions, purulent exudate, periductal inflammation and interstitial pancreatitis. Bicarbonate concentration was depressed to 67 mEq./l. Volume and amylase were within normal limits. Here the liver pathology was reported as Grade IV. In another patient (Case 19) the pancreatic pathology was read as an occasional ductule distended with dense homogenous material, degenerative epithelium and an appearance of duct ectasia with squamous metaplasia of the epithelium. But the parenchyma was reported as negative. This patient had normal volume, a bicarbonate concentration of 80 mEq./l and an amylase of 3.4 units/kg. Again, the liver pathology was reported as Grade IV cirrhosis. The deaths in the last two patients were due to hemorrhage, progressive liver failure with jaundice in one and in the other; chronic brain syndrome with edema. Obviously, in this very small number of patients no general conclusions can be drawn but it does suggest the lack of correlation between presently accepted standards of function and pathology.

In this study no firm conclusions can be drawn of the relationship between pancreatic disease and portal cirrhosis. Although the primacy of pancreatic disease in the causation of portal cirrhosis has been espoused by some, the contention of most investigators that the same factors of alcoholism and malnutrition produce cirrhosis and pancreatitis appears to follow from the large volume of accumulated clinical and experimental data. Both factors are well recognized as causes for the development of chronic pancreatitis and portal cirrhosis. Constitutional, nutritional and developmental factors, structural alterations, enzymatic differences may all play a role in the tolerance thresholds of these two vital organs to noxious substances.

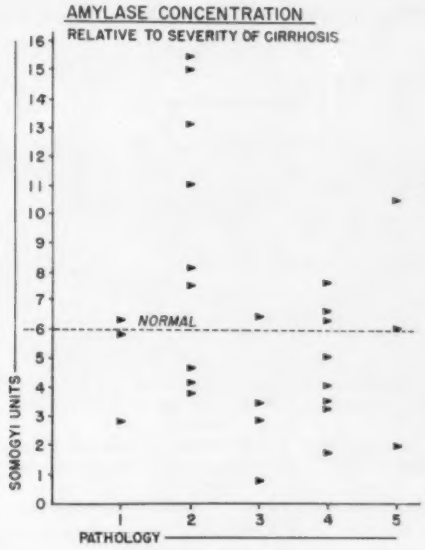

Fig. 3

Steatorrhea in these patients was not studied. The amount of digestive dysfunction was not expressed in any but clinical fashion.

Summary

1. Twenty-five patients with alcoholic (nutritional) cirrhosis (portal) were studied by means of the secretin test to determine the values of exocrine pancreatic secretions.

2. Although pancreatic function was not uniformly depressed, the majority of patients in this series revealed some evidence of pancreatic dysfunction. There was no firm correlation between the severity of the pathologic process in the

liver and the depression of pancreatic function as expressed in volume, bicarbonate and amylase concentration.

3. The most significant depression of pancreatic function was found in the values for bicarbonate concentration. Depression of amylase concentration followed closely but volume was abnormal in a much smaller percentage of patients. All three values were not uniformly depressed although associated abnormalities in bicarbonate and amylase concentration were found in a majority of those patients with positive findings.

4. The extent of pancreatic dysfunction as determined by exocrine secretion did not consistently reflect the severity of pancreatic pathology in four patients studied at necropsy. Nor did the degree of liver disease correlate with pancreatic pathology.

ACKNOWLEDGMENT

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HUMAN BILIARY-PANCREATIC SECRETION*

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Physiologically significant measurement of human bile and pancreatic juice was made possible by collecting the total output at frequent intervals during the 24-hour period, and reinjecting the secretions after measurement. This was achieved in patients eating three meals a day, and having the freedom of the ward. Bile or pancreatic juice was collected at two-hour intervals, and after keeping a small aliquot, the rest was reinjected through a special T-tube or

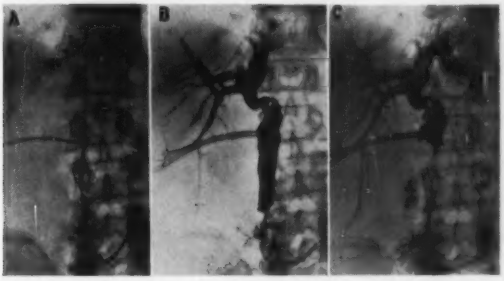

Fig. 1—Special T-tube for total bile collection: The distal section of the tube is shown filled with Urokon (A). It empties into the duodenum directly. In (B), the proximal portion has been injected, filling the biliary tract, and flowing around the distal part of the tube into the duodenum. In (C), the balloon around the distal part of the tube has been distended, obstructing the duct. Such a tube permits total bile collection through the proximal part, and reinjection into the duodenum through the distal part. This tube should be inserted only after sphincterotomy.

through a gastrostomy tube. Due to the lability of the enzymes in pancreatic juice, it was collected in an iced container and the aliquots placed immediately in the deep freeze. After the 24-hour collection was completed, the aliquots were combined into one 24-hour sample.

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Methods and Analytical Procedures

The total bile output was collected by means of a specially designed T-tube (Fig. 1), which prevented loss of bile into the intestinal tract and permitted reinjection of each sample into the duodenum[1]. If pancreatic juice was being collected in the same individual, this juice could also be injected directly into the duodenum. The pancreatic juice was collected by means of a plastic tube inserted into the duct of Wirsung after section of the sphincter of Oddi[2]; loss of juice into the duodenum around the tube was prevented by the presence of a tiny water-inflated balloon surrounding the end of the tube (Fig. 2). Such an experimental set-up was possible only in patients lacking a functioning accessory duct of Santorini.

Fig. 2—Special tube for total pancreatic juice collection: The plastic tube, fitted near its tip with a small balloon, is inserted into the pancreatic duct after sphincterotomy. After blowing up the balloon (arrow), the tube is fastened at its exit from the duct to the posterior lip of the sectioned papilla, and is then brought up to the abdominal surface, through the common and cystic ducts. If the gallbladder is absent, it is attached to the T-tube in the common bile duct, and brought out alongside. In the absence of an accessory duct, the total pancreatic juice can be collected.

Bile was analyzed for bile salts, by a modification of the method of Mosback[3]; cholesterol by a modification of the method of Zlatis et al[4]; pancreatic juice was analyzed for bicarbonate, amylase[5], lipase (by a modification of the method of Seligman[6]) and total proteolytic enzymes using a casein substrate and a trypsin standard[7]. Recently, by the use of specific substrates, methods were developed for the quantitative estimation, in pancreatic juice, of trypsinogen and trypsin, chymotrypsinogen and chymotrypsin, procarboxypeptidase A and carboxypeptidase A, as well as desoxyribonuclease. In this paper, only the volume and bile salt concentration of bile, and the volume, amylase, lipase and

total proteolytic enzymes of pancreatic juice was presented. Since our experience had shown that the various pancreatic enzymes, collected directly from the ducts, were secreted in parallel concentration, and this parallelism was not affected by diet or disease, only the results of amylase analyses were presented in many cases.

Material

Bile:—Two hundred thirty-eight 24-hour collections were made on 22 patients. The effect of diet, choleretics, secretin, and various other drugs was studied. A great many isolated samples of gallbladder and liver bile were analyzed.

Pancreatic juice:—Seventy-five 24-hour collections on 38 patients were analyzed. The effect of diet, acid, and various drugs on pancreatic juice was studied.

TABLE 1

Human Biliary Secretion: Example of Typical 24-hour Output

Volume ml.	1030	Cholic acid gm.	7.01
Phospholipid gm.	0.54	Deoxycholic acid (s) gm.	4.53
Sodium mEq.	152	Cholesterol gm.	2.10
Potassium mEq.	4.8		

Many isolated samples of pancreatic juice, as well as three-hour collections, were analyzed.

Results

Bile:—1. Total output: Total 24-hour output of bile from apparently normal livers varied between 1,000 and 2,000 ml. Livers subjected to varying periods of partial or complete biliary obstruction secreted volumes as low as 400 ml. A typical analysis is presented in Table I.

2. *Effect of choleretics:* An example of the secretion from an apparently normal liver is presented in Fig. 3. The total volume for 24 hours was 1,500 ml. and the total bile salt output 10 gm., half cholic acid and half deoxycholic acid. One and a half gm. Zanchol (a choleretic) was given; the volume rose slightly on the second day, but the total bile salts fell. When administration of this drug

was stopped there was a rebound in the output of bile salts to 14 gm. Administration of 1.5 gm. of dehydrocholic acid for two days raised the volume only

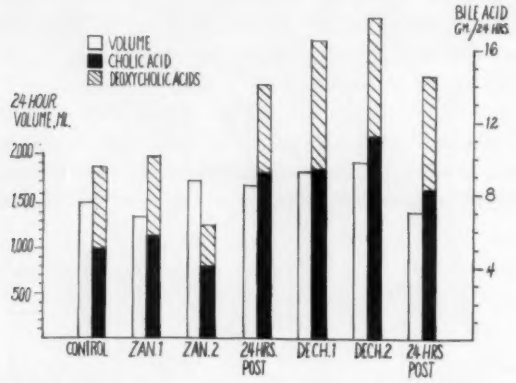

Fig. 3—The 24-hour biliary secretion in a patient with a normal biliary tract: The control column represents the basic secretion two weeks postoperatively. Zanchol (Zan.) was administered with meals in three doses of 0.5 gm. Decholin (Dech.) was administered in similar dosage.

slightly by the second day, but the total bile salts rose to 18 gm. Twenty-four hours later, the volume fell to 1,300 ml. but the total bile salt output fell only slightly, to 14.5 gm.

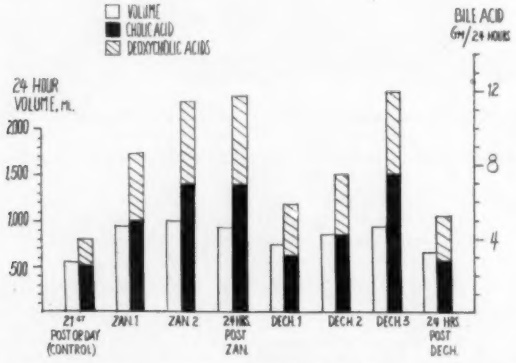

Fig. 4—The 24-hour biliary secretion of a patient who had a partial obstruction due to choledochal stones: The first control column shows the output on the 21st postoperative day. The response is shown to Zanchol (Zan.) and to Decholin (Dech.) given for two days in dosage of 0.5 gm. three times a day.

3. *Effect of obstruction:* A patient who had partial obstruction due to multiple choledochal stones had a basic 24-hour secretion of only 550 ml., con-

taining 4 gm. bile salts, two-thirds of which was cholic acid (Fig. 4). Zanchol produced a marked response, the volume rising to 1,000 ml. and the bile output to 12 gm. This was maintained 24 hours after administration of this drug was

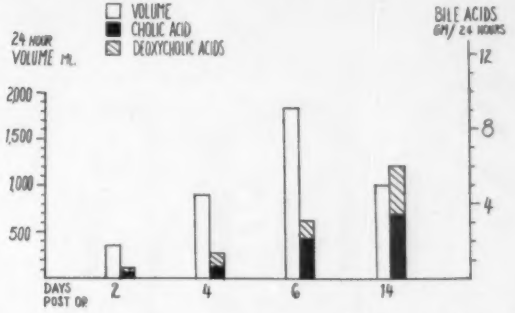

Fig. 5—The 24-hour biliary secretion of a patient with common duct obstruction due to pancreatitis: The recovery of hepatic function is shown by the analyses of the bile output on the indicated days following relief of the obstruction by sphincterotomy. Note recovery of volume (on the sixth day) occurred before the increased secretion of bile salts.

stopped. In this patient the choleretic effect of dehydrocholic acid was achieved more slowly, and the 24-hour output after cessation of administration of dehydrocholic acid dropped more rapidly.

Relief of complete biliary obstruction was followed by a slow return of volume and bile salt output (Fig 5). It requires 10 to 14 days for secretion of

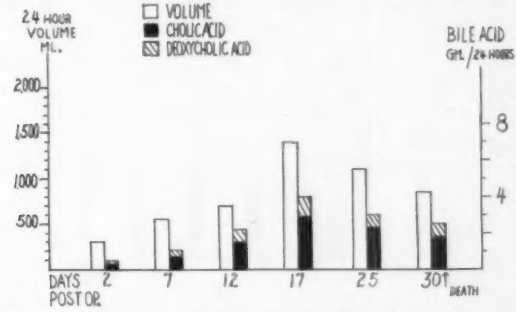

Fig. 6—The 24-hour biliary secretion of a patient following relief of common duct obstruction due to carcinoma of the head of the pancreas (with metastases to the liver): Note gain (on seventh day) of volume before increase of bile salt output. Biliary secretion continued until the day patient expired from metastatic growth.

bile salts to return to a permanent (low) level. Typically, the volume tended to rise rapidly and excessively before the bile salt output returned adequately (Day 6, Fig. 5). This same slow return to normal volume and bile salt output, after

relief of obstruction, was seen in a case of carcinoma of the head of the pancreas, with complete biliary obstruction and metastases to the liver (Fig. 6).

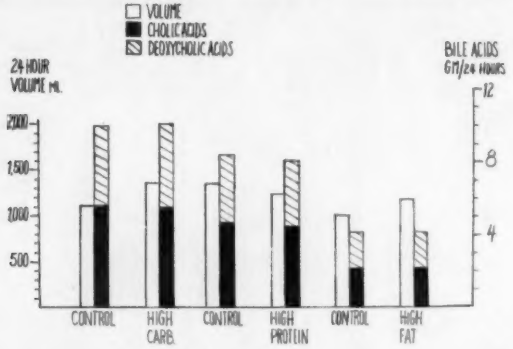

Fig. 7—The response of biliary volume and bile salt output to various diets: Patients with normal livers and biliary tracts were stabilized and 24-hour control samples taken. Diets, consisting principally of either carbohydrates (carb.), protein, or fat, were fed for a 24-hour period. During this period the bile was collected and analyzed. Note that over a 24-hour period the output did not vary with the diet.

It was noted that the secretion tended to return to normal values on the seventeenth postoperative day, 13 days before death.

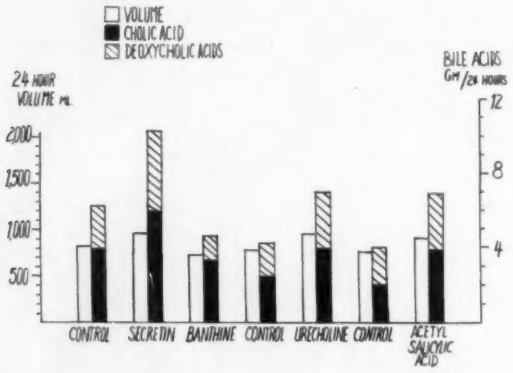

Fig. 8—The biliary response of the liver to drugs: Two patients with previous biliary obstruction were allowed to stabilize (at least 14 days postoperative) and 24-hour control collections made. The response to the following drugs was studied: Secretin (Lilly)—100 clinical units given three times a day intravenously; Banthine (Searle), 50 mg. orally three times a day; Urecholine (Merck), 5 mg. orally three times a day; and aspirin, 10 grains, four times a day.

4. *Effect of various foods and drugs:* Studies showed that diets containing pure carbohydrates or pure proteins or pure fats, given for at least 24 hours,

had no influence on the volume, or bile salt concentration, of the biliary secretion (Fig. 7). Secretin (100 clinical units) given intravenously three times during the day, increased both the volume, and especially the bile salt output (Fig. 8). Banthine (50 mg. three times a day), reduced the volume and bile salt output

TABLE II

HUMAN PANCREATIC SECRETION: EXAMPLE OF TYPICAL 24-HOUR OUTPUT

Volume ml.	1,486	Amylase Lagerlöf units	21,100
Bicarbonate mEq.	116	Total proteolytic activity as mg. trypsin	227
Sodium mEq.	225	Active trypsin mg.	0.27
Potassium mEq.	8.1	Lipase, mEq. ester split (β-naphthyl laurate)	5,430

(Fig. 8). Both Urecholine (5 mg. orally, three times a day) and aspirin (a total of 2.4 gm. during the day) increased the volume and especially the total bile salt output (Fig. 8).

TABLE III

HUMAN PANCREATIC SECRETION: EXAMPLE OF HIGH 24-HOUR OUTPUT

Volume ml.	2,711	Amylase Lagerlöf units	32,670
Bicarbonate mEq.	324	Total proteolytic activity as mg. trypsin	1,274
Sodium mEq.	—	Active trypsin mg.	0.54
Potassium mEq.	—	Lipase, mEq. ester split (β-naphthyl laurate)	13,826

Pancreatic juice:—1. Total output: The total 24-hour volume of pancreatic juice secretion varied from 1,500 to 4,000 ml. The latter high volume was exceptional since we observed only two such patients. Generally, if the pancreas appeared normal by our criteria, the volume averaged 2,500 ml. Examples of low

and high analyses are shown (Tables II and III). The extraordinarily high output of bicarbonate should be noted. Normal juice always contained a trace of active trypsin. This was sufficient to activate the proteolytic enzymes and to cause them

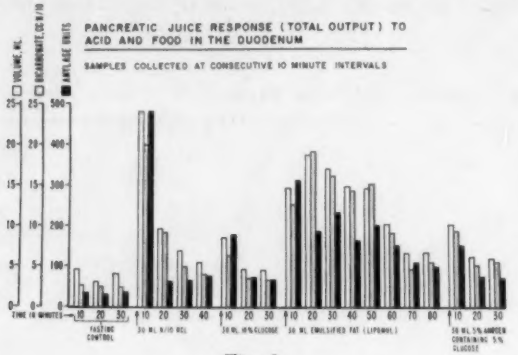
PANCREATIC JUICE RESPONSE (TOTAL OUTPUT) TO ACID AND FOOD IN THE DUODENUM
SAMPLES COLLECTED AT CONSECUTIVE 10 MINUTE INTERVALS
VOLUME, ML.
BICARBONATE, EQ N/10
AMYLASE UNITS
TIME IN MINUTES
FASTING CONTROL
30 ML N/10 HCL
30 ML 10% GLUCOSE
30 ML EMULSIFIED FAT (LIPOMUL)
30 ML 5% AMIGEN CONTAINING 5% GLUCOSE

Fig. 9

to digest themselves as well as the lipolytic enzymes in pancreatic juice standing even for one hour at room temperature.

2. *Effect of hydrochloric acid and foods:* The effect of acid, pure glucose, pure protein and pure emulsified fat, injected into the duodenum through a Rehfuss tube, is presented in Figure 9. It was noted that in this case, the fasting

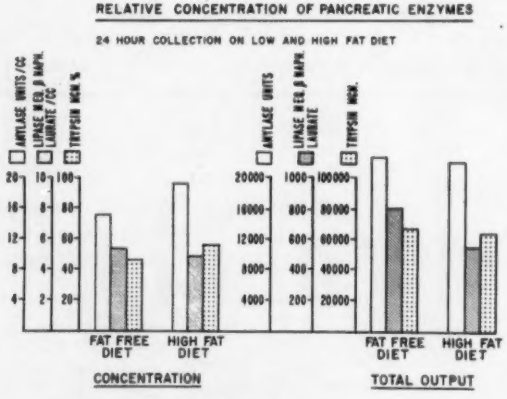

Fig. 10

pancreas secreted 3 to 5 ml. every 10 minutes. Injection of N/10 hydrochloric acid, raised the volume to 25 ml., and the bicarbonate and enzymes proportionately. The effect wore off in 40 minutes. The influence of glucose and of amino acids (Amigen) was milder, but the stimulation produced by emulsified fat

(Lipomul) was more marked and still persisted after 80 minutes. This might have been due to the fact that the duodenum retained the fat for a longer period of time. Nevertheless, administration of low-fat or high-fat diets for 24 hours made no difference either in the volume or the enzyme content of pancreatic juice secretion (Fig. 10). Nor did feeding of either high-carbohydrate, high-protein, or high-fat diets for a period of a week have any influence on the three-hour collection of pancreatic juice after each period (Fig. 11).

3. *Effect of anticholinergic drugs:* Banthine was more effective than atropine in suppressing the secretion of pancreatic enzymes (Fig. 12). This suppressive action of Banthine was obvious even in patients who were fed. The response of the duodenum to instillation of hydrochloric acid, was inhibited by atropine, Pro-Banthine, and Pamine (Table IV). The effect of Pamine is graphically illustrated in Fig. 13.

TABLE IV

EFFECT OF ANTICHOLINERGIC DRUGS ON RESPONSE OF PANCREAS TO INSTILLATION OF 30 ML. N/10 HYDROCHLORIC ACID INTO DUODEUM

Patient	Control	HCl	Drug (intramusc.)	Response to HCl instilled ½ hr. after drug	% Reduction
1. Volume: *In 30-minute increments*					
H.A.	4.2	23.4	Atropine (0.3 mg.)	9.4	60.0
J.J.	5.0	17.0	Pro-Banthine (30 mg.)	4.0	76.5
F.H.	7.2	87.0	Pamine (1.0 mg.)	18.4	79.8
2. Total amylase (Lagerlöf units): *In 30-minute increments*					
H.A.	11.0	37.5	Atropine (0.3 mg.)	17.2	55.0
J.J.	81.2	161.3	Pro-Banthine (30 mg.)	78.6	51.0
F.H.	232.0	2148.0	Pamine (1.0 mg.)	108.0	95.0

COMMENT

The ultimate aim in medicine is to characterize normal and abnormal physiological phenomena quantitatively. This report presents our attempts to achieve this with bile and pancreatic juice in man.

The bile salts normally secreted into the intestine are reabsorbed to the extent of 90 per cent and re-excreted by the liver, thereby stimulating the formation of more bile. When bile is lost through a fistula, this enterohepatic circulation of bile salts is terminated and the liver has to produce anew each day the bile salts secreted. Under these circumstances the total daily bile secretion amounts to 400-600 ml. The technic described here maintains the normal enterohepatic circulation, relieves the liver of the necessity of producing new bile salts daily, and maintains the normal digestive process. Under these physiological circumstances, human secretion amounts to 1,000-2,000 ml., containing

10-15 gm. of bile salts. These figures are much higher than the value of 500 ml. ordinarily stated in text books[8].

The major bile salts are cholic and deoxycholic acid (combined largely with taurine and glycine) in approximately equal proportions. These values are similar to the results reported previously using a different method for bile salt analyses[9,10]. There is some suggestion that the major part of the bile salt, reported as deoxycholic acid, is actually chenodeoxycholic acid, an isomer of deoxycholic acid which can be detected only by complicated chromatographic procedures[11].

The effect of obstruction and fibrotic replacement of destroyed tissue is to reduce the daily output of bile by the liver. Partial and complete obstruction for any length of time reduces the biliary output to a volume as low as 400 ml.

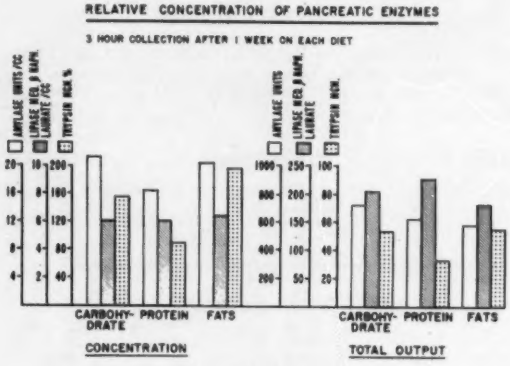

Fig. 11

This output is achieved postoperatively after a period of two to three weeks. It should be noted that recovery occurs first in volume and then in bile salt output (Fig. 5).

Choleretics such as Zanchol and Decholin (dehydrocholic acid) have a marked measurable effect on the daily output both of bile and of bile salt content. Secretin, Urecholine, and aspirin also are definite choleretics. Anticholinergic drugs such as Banthine, diminish the volume of biliary secretion. The mechanism is unknown.

It is noteworthy that variations in the diet have no influence on the daily volume and bile salt output of the liver.

The capacity of the pancreas to produce pancreatic juice is remarkable. Although advanced disease reduces the volume markedly, the apparently normal gland can produce 1,500-3,000 ml. of pancreatic juice in 24 hours. Measurement

in two of our patients showed a daily secretion of 4,000 ml. These findings are far greater than the figure of 700 ml. quoted in the literature[12].

The electrolyte concentration of such large volumes of fluid explains the serious and frequently rapidly lethal effect that follows loss of pancreatic juice either through fistulas or as a result of prolonged vomiting. The large amount of sodium bicarbonate secreted by the pancreas helps to achieve an optimum pH for the proteolytic enzymes and lipase. Administration of enteric-coated bicarbonate along with pancreatin in pancreatic juice deficiency has been shown to enhance the absorption of fat from the intestinal tract[13].

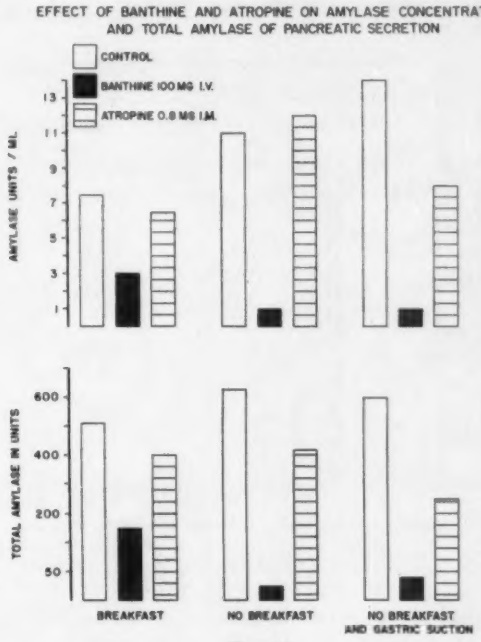

Fig. 12

Patients subjected to effective nasogastric suction and atropine administration, postoperatively, frequently do not secrete any pancreatic juice or at most 5-10 ml. a day. Patients who are not fed will secrete small quantities of juice due to the entrance of hydrochloric acid into the duodenum. Injection of N/10 hydrochloric acid into the duodenum stimulates secretin and pancreozymin production. As a result, there is a sharp rise in the volume of pancreatic secretion which subsides in about 30 minutes. Pure glucose or pure amino acids produce less secretion. The most marked effect is produced by fat in the duodenum. The resultant enhancement of secretion lasts more than 80 minutes and may

be due either to a specific effect of fat or to the fact that fat remains for a long time in the duodenum. Nevertheless, the feeding of large amounts of fat either for 24 hours or for a period of a week, does not have more effect on the volume or enzyme output than the similar administration of either carbohydrate or protein. These findings do not support the observations of Grossman et al[14], that various diets influence the composition of pancreatic enzymes. They, however, used rats, and analyzed the pancreatic tissue for enzymes after a three-week period on pure diets.

The anticholinergic drugs reduce both the volume and enzyme output in the human. This effect is most marked in the absence of food intake but is definite even if the patient is fed. The newer drugs such as Banthine, Pro-

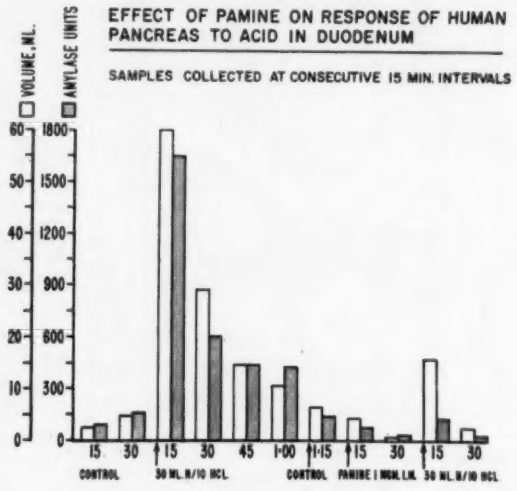

Fig. 13

Banthine, and Pamine are more effective than atropine, but their side-effects, such as the paralysis of the urinary bladder, or the rapid pulse that often accompanies their administration, mitigates against their routine use postoperatively. Their action in reducing the response of the human pancreas to the intraduodenal administration of hydrochloric acid confirms the observation of Ivy[15] and Thomas[16]. It does not, however, clarify any further the ultimate mechanism of hormonal stimulation.

Summary

1. The human produces 1,000-2,000 ml. of bile every 24 hours, containing 10-15 gm. of bile salts. The major bile salts, cholates and deoxycholates, are

secreted in approximately equal amounts. Prolonged obstruction of the biliary tract reduces both the volume and bile salt content of bile.

2. Choleretics such as Zanchol and Decholin increase the volume and bile salt content markedly. Secretin, Urecholine, and aspirin also are good choleretics. Anticholinergic drugs such as Banthine, reduces biliary secretion.

3. The human produces 1,500-3,000 ml. of pancreatic juice every 24 hours. Besides the enzymes, which are secreted in parallel concentration, a large amount of sodium bicarbonate (10-25 gm.) is present in the pancreatic juice. The importance of the bicarbonate is noted. Disease reduces both the volume and enzyme content of pancreatic juice.

4. Instillation of food or hydrochloric acid into the duodenum increases the flow of pancreatic juice markedly. Anticholinergic drugs reduce this response to a varying degree.

5. Feeding diets containing pure carbohydrate, pure protein, or pure fat, did not influence the volume, bile salt, or enzyme content of bile or pancreatic juice.

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Discussion

Dr. Dale W. Creek (Santa Barbara, Calif.):—I think certainly the last paper by Dr. Doubilet is unique in the sense that many of us for years have been trying to measure pancreatic and bile secretions and we have used duodenal intubation—we've done this in some 10,000 cases in our group and we were impressed with the inaccuracy of our results.

I think that what he has presented here particularly shows us that the figures that we have learned from text books and from other reported sources, must be indeed very low to what actually happens.

In this case he was able to measure actually, accurately, without loss and without the destruction of the various enzymes by the admixture of duodenal contents which we usually achieve. I certainly was most interested in hearing his method of collection by means of this ingenious tube with the inflated balloon. I think his slides demonstrated very graphically just what this method was.

I certainly will be interested in knowing the continuation and follow-up of this. I'm sure that a great deal of time and thought has gone into it before and I don't know what sort of illumination came to him to develop this type of technic, but I think it is something admirable. We are all familiar with his previous work in sphincterotomy and this is basic physiology which adds a great deal to our knowledge of what the pancreas and what the liver secretions are in human beings.

I have very little to say about the previous paper because again with duodenal intubation I am uncertain as to the results that we obtain in measuring amylase, lipase, and proteolytic enzymes.

I certainly would like to compliment both of these men and I'm glad to see so many stayed to hear this at this time.

THE DIAGNOSIS OF COMMON DUCT STONES BY INTRAVENOUS CHOLANGIOGRAPHY COMPARED WITH COMMON DUCT EXPLORATION

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and

HENRY D. FREIMAN, M.D.†

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The introduction of intravenous Cholografin unquestionably has provided another diagnostic tool in the armamentarium of procedures for the clinical evaluation of the biliary tract. Cholografin may be employed for the diagnosis of gallbladder disease. Because, however, of the high index of accuracy obtained by the oral administration of dye tablets, the use of Cholografin is to be considered as an adjuvant rather than as a replacement procedure. It is true that in certain instances where nonvisualization of the gallbladder results after the ingestion of tablets, administration of Cholografin may produce a visualized gallbladder and perhaps calculi[7]. The very small increase in incidence of positive findings by Cholografin may be, for practical purposes, overshadowed by such disadvantages as the cost, the time required to carry out the examination, failure to detect small stones because of the greater viscosity of the Cholografin solution.

During the course of uncovering the many advanatges of Cholografin, one of the outstanding contributions is the ability to investigate the biliary tract in the presence or absence of a gallbladder. An opportunity is provided to determine whether symptoms which persist after removal of the gallbladder are due to disease of the ductal system[4]. Cholografin provides an additional benefit by eliminating the variable factor of intestinal absorption of the dye tablets. It will circumvent the interference imposed by pyloric obstruction[12]. The flow of Cholografin from the common duct into the small intestine may aid in determining the patency of the sphincter of Oddi. Cholografin may, also, be employed to investigate the functioning capacity of an end-to-end anastomoses of the common duct performed for stricture. The diagnosis of biliary dyskinesia may be made by the utilization of Cholografin under proper circumstances[4]. Fistulas have been reported to be recognized after the administration of Cholografin by the appearance of the dye outside the confines of the normal anatomy of the biliary tract. The speed in producing roentgenograms of the biliary duct and gallbladder following the intravenous injection of Cholografin enhances its value where a prompt decision must be made in the presence of an acute abdominal emergency whether the disease is present in the biliary tree[10]. Finally, Cholografa-

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fin has been considered for use preoperatively to augment the examination of the common duct which later may be supplemented by exploration and operative cholangiography. This study was conceived, therefore, to evaluate the degree of accuracy of roentgen diagnosis of the common duct opacified by Cholografin. The investigation was limited to the abnormality of stones in the common duct.

The patients selected for this series consisted of those who clinically had evidence of biliary tract disease, who later were operated upon, and whose common duct was explored after consideration of appropriate indications. Many of these patients had preoperative cholangiograms. The comparison was made whenever a patient had both common duct exploration and an intravenous cholangiogram. Only the roentgen studies which were accepted as being diagnostic for presence or absence of common duct stones were used for comparison.

Results

There were 55 patients in whom a diagnosis of a normal common duct was made following intravenous Cholografin. The common duct exploration in this group of patients revealed that in 11 cases or 20 per cent, stones or gravel were found in the common duct. In every instance where a stone was found, it was described as being very small in size. The presence of gravel in the common duct was considered to be a positive finding as though a stone was present. In 2 cases a report of a normal common duct following Cholografin opacification revealed by operative cholangiography that a stone was present in the common duct. Common duct exploration was not carried out in these 2 cases. In this group of 55 cases of normal common duct reported as such by the Cholografin study, operative cholangiograms were carried out in 53 cases. The difference of 2 cases is explained by the fact that 1 operative cholangiogram was not performed and the second was considered to be unsatisfactory for diagnostic purposes. In the 50 cases in which a comparison could be made, stones were found in 3 cases or 5 per cent which were not demonstrated following the nonoperative technic.

In a group of 18 cases, intravenous cholangiography demonstrated the presence of stones in the common duct. Following common duct exploration in this series, stones actually were found in 13 or 72 per cent of cases. In 3 instances, a widened common duct was recognized following intravenous Cholografin, but no stones could be visualized. Stones, nevertheless, were found in 2 cases on common duct exploration. In the third case no stone could be seen.

In this group of cases operative cholangiography was carried out as a check on common duct exploration rather than on the report of the intravenous or preoperative study. As a result, this comparative study must be considered as a postoperative cholangiographic review. Stones were found by operative cholangiography in 5 cases after the common duct exploration had been completed and no stones found.

Comment

The limitations of intravenous cholangiography have been recognized. Inability to obtain satisfactory visualization of the biliary tract in the presence of jaundice handicaps the fullest potential value of the examination. The presence of significant liver damage without jaundice will interfere with a completely adequate x-ray study[6]. All too often nonopaque calculi in the larger bile ducts have escaped detection while opaque stones less than 1 cm. in diameter similarly may be unrecognized. There has been consistent failure to visualize the terminal portion of the common duct, an area which continues to be a blind spot despite many attempts of new technics to delineate it more clearly.

According to this study it seemed apparent that small stones or gravel which were present in the common duct were not detectable by roentgen examination. Gravel may not rightfully be considered in the same category as calculi but was considered as such since it alone was present in the common duct of patients who presented symptoms of biliary colic. With full understanding, gravel in the common duct may have been a coincidental finding when the active site of pathology might have been elsewhere, such as, in the gallbladder.

Two cases in this series were not included in the statistics because in each case the common duct was not considered to be visualized sufficiently well to be considered a diagnostic study. Nevertheless, stones were found on exploration of the common duct and on operative cholangiography. It might be pointed out that the cases in this study were selected only if a completely satisfactory or diagnostic examination was obtained. According to some authors as high as 30 per cent of cholangiograms are considered to lack sufficient clarity to exclude ductal stones with reasonable certainty! The criteria by which a study can be considered diagnostic depends on definition, with regard to intensity of opacification, completeness of filling of the common duct, and avoidance of intestinal gas shadows, etc. The mere recognition of the presence of a common duct should not be accepted as providing the necessary information upon which a conclusion can be rendered as to the presence or absence of common duct abnormality. Obviously, statistics to measure the accuracy of nonoperative cholangiographic studies will depend upon the quality of each examination.

The relatively high percentage of correlation between the identification of stones in the common duct following nonoperative cholangiography and those detected in common duct exploration supports the value of Cholografin as a preliminary study. There may be reason for speculating that the correlation between nonoperative cholangiography and the findings at common duct exploration may be closer if the belief is accepted that small stones frequently pass from the common duct into the duodenum[5].

Whereas positive findings in the well-visualized common duct may be considered helpful in establishing a diagnosis, the poorly visualized common duct

or a nonvisualized common duct offers no aid even by indirect or circumstantial conclusions which sometimes is obtained from a nonvisualized gallbladder.

The reliance upon circumstantial features in attempting to establish a diagnosis of a stone in the common duct may lead to erroneous conclusions. The secondary findings may be found in the size of the common duct. Recent study of the relation of the size of the common duct and the actual presence of stones in the common duct led to the conclusion that some bile ducts not containing stones were as large as any that did contain stones[5]. At the same time almost 75 per cent of common bile ducts which contain stones were between 7 and 11 mm. in diameter. According to the established standard, this is close to the accepted normal size of a common duct. The delayed emptying of the dye from the common duct into the duodenum is another inference which may prove to be misleading.

On the basis of this study the detection of a stone in the common duct by Cholografin offers a strong likelihood that the stone is present. Because there is less than complete reliability on the appearance or absence of a stone in the common duct by preoperative methods, additional measures for proving the diagnosis must be carried out. Operative cholangiography as well as surgical exploration of the common duct should be employed since neither is infallible as an independent study[8]. In this way an attempt at total effectiveness in ruling out disease of the common duct in the form of stones may be more closely approached.

Summary

In a group of 55 cases, in which the common duct was reported to be normal following the administration of Cholografin, stones were found in 11 instances, or 20 per cent, by common duct exploration.

By intravenous cholangiography, choledocholithiasis was reported in 18 patients. After common duct exploration, stones were found in 13 patients or 72 per cent.

Common duct stones which are detected by intravenous cholangiography in diagnostically acceptable examinations are likely to be found on surgical exploration.

A strongly suspected clinical diagnosis of choledocholithiasis should not be ruled out by the report of a normal intravenous cholangiogram.

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Coca-Cola, too, has its place in a well balanced diet. As a pure, wholesome drink, it provides a bit of quick energy ... brings you back refreshed after work or play. It contributes to good health by providing a pleasurable moment's pause from the pace of a busy day.

CINEGASTROSCOPY*

II. External Source of Light for Color Cinematography Through the Gastroscope

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and

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The two major methods of visual observation of gastric function are radiography and gastroscopy. In recent years cineradiography has supplemented fluoroscopy and standard radiography. Motion picture strips which permit examination by a group of investigators are far superior to the most detailed description of an individual's fluoroscopic findings and to the analysis of single radiographic films. Cineradiography affords objective documentation of motion and adds a new dimension to the study of gastrointestinal function in health and in disease. Similarly, gastroscopy and still color photography through the gastroscope can now be supplemented by color cinematography. The term, cinegastroscopy, was proposed by us[1] to describe the technic of obtaining color motion pictures through the gastroscope. This paper is an analysis of some of the problems, solutions, and potentialities of cinegastroscopy.

The chief obstacle in obtaining color motion pictures through the gastroscope has been the difficulty of achieving sufficient intragastric illumination for proper film exposure.

High levels of illumination are required since only 1 or 2 per cent of the light incident on the objective lens reaches the eye-piece. This large loss of light is the result of absorption by the many lenses of the flexible gastroscope and of reflection at the various lens interphases. No other endoscopic instrument places such stringent demands on the light source.

A new method was devised for high intensity illumination of the stomach interior. A bundle of fiberglass was incorporated into the gastroscope to serve as a flexible light "carrier" from an external source to the stomach. This flexible light "carrier" was fitted with a mirror system placed near the objective. By mounting a reflex movie camera at the ocular and by using a highly sensitive

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*Presented in part at the Annual Meeting of the American Gastroscopic Society, New Orleans, La., 30 March 1960; and the New York Academy of Gastroenterology, 25 April 1960.

From The Columbia University Research Service, Goldwater Memorial Hospital, and the Departments of Medicine and Surgery, College of Physicians and Surgeons, Columbia University, New York, N. Y.

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color film, it was possible to obtain color motion pictures at eight frames per second.

Selection and Mounting of Components

The light "carrier":—An extremely flexible small diameter device for efficiently transmitting light over a distance of approximately 125 cm. was needed. Two possible carriers were considered: lucite and glass fibers.

Cast lucite, as distinct from extruded lucite, transmits light efficiently. The difficulties of obtaining cast lucite of small diameter (expensive dies and tools, and the fragility of lucite which prevents machining) automatically eliminated this choice. Instead, bundles of glass fibers were obtained from the American Optical Co. Each individual fiber, 0.002 inch in diameter, is coated with a layer of glass of a lower refractory index. Because of this difference in refractory indices, light incident on the proximal end undergoes repeated internal reflections and is emitted at the distal end (Fig. 1). By testing, it was determined that approximately 80 per cent of the light entering the proximal end is emitted

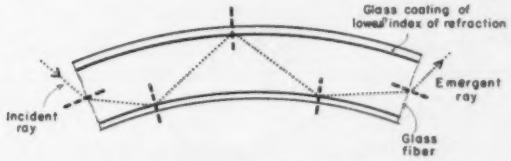

Fig. 1—Light transmission through a glass fiber.

at the distal end. The fiberglass bundle was inserted into the biopsy lumen of the Benedict operating gastroscope (American Cystoscope Makers, Inc.). The size of the lumen limited the diameter of the bundle to a maximum of 0.09 inches. The distal deflecting unit of the operating gastroscope was removed and replaced by a mirror which reflects the light transmitted through the bundle onto the viewed stomach interior. A plastic cover was used to protect the mirror and the distal end of the bundle of fiberglass (Fig. 2).

Light Source and Its Coupling to the Fiberglass Bundle

The external light source had to be focused efficiently onto the small cross-sectional area of the fiberglass bundle. The logical choice appeared to be a tungsten filament source with a light weight condensing system. The Sylvania Truflector bulb (150 watts) was selected. Its efficient focusing is accomplished by a mirror mounted in the bulb immediately behind the filament. An additional lens, a heat-resistant glass, and a cooling fan were mounted for improved focusing and protection of the proximal end of the bundle. Even with this extra lens, only 25 per cent of the usable light enters the bundle because of its small cross-sectional diameter (about 2 mm.).

Camera and Film

A Camex 8-mm. reflex camera was used. It has a reciprocating mirror that permits the gastroscope image to impinge alternately on the film and on the viewing system. The gastroscopist, when viewing, sees the usual image slightly magnified and, when filming, sees a flickering image. At eight frames per second the flicker is not disturbing. A fixed focus, 12.5-mm. lens reduces the image to approximately the regular frame size of an 8-mm. film.

The new Eastman Kodak high-speed color reversal film, SO 270 type B, was made available in 8-mm. size. Adequate color filming through the gastroscope was thus possible at eight frames per second.

Results

With the above instrument several studies were performed on the stomach model constructed by the Cameron Company for teaching gastroscopy. Ade-

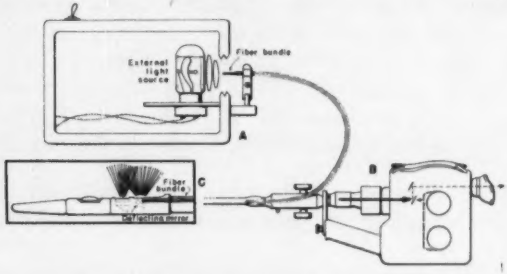

Fig. 2—Cinegastroscope with external light source (A), the fiberglass bundle serving as a flexible light carrier to the deflecting mirror situated proximally to the objective lens (C) and the reflex camera (B).

quate color reproduction was obtained with the objective at distances of 2 to 10 cm. from the simulated lesions. Only one patient was examined with this instrument in order to prove that adequate illumination and color reproduction could be obtained. When projected with standard projectors, at 16 frames per second or faster, there was excellent reproduction of motion. Further use of this equipment awaits construction of permanent models by makers of gastroscopes.

Future Modifications and Applications

The method of cinegastroscopy with external light source and flexible light carrier could be improved by incorporating additional modifications.

In a newly designed gastroscope with provisions for a larger cross-sectional area of fiberglass, a smaller light bulb could be mounted directly on the gastroscope near the ocular, thereby eliminating the need for the bulky light accessory.

By removing the rubber finger and the distal bulb one can build an instrument with either "end-on" viewing or lateral viewing. Such a terminal objective could be advanced into the antrum by a guidance system[2] and allow close inspection of the lesser curvature of the antrum and the entire prepyloric area.

The projected model should thus have the following characteristics: 1. The lens system can be similar to those used in the present instruments, 8-9 mm. in diameter. 2. There should be provision for two channels running alongside the lens system, one to include the fiberglass bundle with sufficient protection and freedom of motion to remain flexible and allow sliding within the channel during flexion of the gastroscope, the other to be used for air insufflation and the guidance system; the use of the guidance system will eliminate the need of the rubber finger for passage through the gastroesophageal segment.

Summary and Conclusions

An experimental gastroscopic unit was developed for color cinematography at eight frames per second with an external source of light and a flexible light carrier.

Results of studies in a stomach model and in one patient have shown that color motion pictures through the gastroscope with a highly sensitive film give excellent reproduction of color and motion.

This method of objective documentation can be utilized for investigations of gastric function in health and in disease and particularly for gastroscopic diagnosis.

In addition, a new type of instrument is proposed for improved visualization of the "blind areas" and color cinematography.

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BENEFICIAL EFFECTS OF ADMINISTRATION OF LACTOBACILLUS ACIDOPHILUS IN DIARRHEAL AND OTHER INTESTINAL DISORDERS

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and

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For a long time, physicians have attempted to use certain bacteria for treatment. The first systematic use of a lactic acid-producing bacillus as soured milk, was by Metchnikoff[1], who believed that Bulgarians using bulgaricus milk lived longer than parts of the population who did not use it. Later, Rahe[2] demonstrated that lactobacillus acidophilus differed from bulgaricus principally by the fact that its natural habitat was the human intestine, and that bulgaricus was a variant which, possibly by reason of long culture in milk, had lost its ability to survive in the gastrointestinal tract.

The gut contains a complex ecological system of anaerobic and aerobic organisms, a number of which live there in symbiosis with their host, i.e. at mutual benefit. It is known now, that they play a vital role in synthesizing certain essential nutrients[3]. It is known, also, that different strains of intestinal bacteria live together in a certain equilibrium. Conditions upsetting this equilibrium, for example, are typhoid and bacillary dysentery and the presence of particular strains of *B. coli* and more recently the vexing problem of antibiotic side-effects has developed. A number of antibiotics, by killing normally occurring intestinal bacteria, allow pathogenic bacteria, yeasts, and fungi, to abnormally overgrow and cause disease. This overgrowth may have serious implications, not the least of which is the production of ammonia, especially by gram negative organisms. This may play a grave, even lethal role in cases of cirrhosis of the liver. Phear and Ruebner[4] have emphasized that lactobacilli are the only intestinal germs which do not produce ammonia.

Recently, epidemics of diarrhea have occurred in Chicago. The onset of the disease was sudden, often with violent diarrhea, intestinal cramps, gas, nausea, and vomiting. In a number of cases, dehydration, prostration, and fainting, occurred. In the majority of cases no pathogenic organism could be cultured from the stools, and it is assumed that these were viral diarrheas, possibly due to an Echo-type of virus. The course of the sickness was 24 hours to one week, rarely followed by recurrence. A number of drugs were tried, including pectin with kaolin, paregoric, etc., but they were of little help, and none abolished the symp-

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toms completely. A possible exception was a certain pectin with kaolin and an anticholinergic preparation, which is under investigation.

Increasing numbers of patients with postantibiotic diarrheas are being seen by the authors. These are often of a more chronic nature than the epidemic cases described above and are more resistant to therapy.

Our attention was called to the possibility of an upset in the equilibrium in the intestinal flora in these cases of diarrhea, and we decided to use a preparation of dried but viable lactobacillus acidophilus, which was supplied to us under the trade name of "Bacid" by the U. S. Vitamin and Pharmaceutical Corporation. We have employed this preparation mainly in the categories described above, but also in a few cases of other diseases mentioned below.

Warnings in the literature of frequent disturbing and occasionally disastrous effects of antibiotics on intestinal flora, with overgrowth of noxious bacteria are too numerous to report here. But it was emphasized by Flippin and Eisenberg[5] that when susceptible germs die, resistant and often pathogenic organisms may overgrow. One way this may come about is by loss of nutritional substances manufactured by beneficial bacteria, but action of bacterial toxins may play a dominant role. One automatically comes to the question of reinstituting a normal bacterial flora. This has been attempted by others with the use of enemas or tube feedings with fecal materials, with obvious difficulties and dangers. A simpler method is to prime the gut with lactose or with casein in any form and to add live lactobacilli. This is done satisfactorily, albeit temporarily, by fermented milk, as yogurt, buttermilk, acidophilus milk, etc.[6-10].

A still simpler and more reliable method[11,12] avoids the lability of these milk products by using a stable, dried, viable culture of lactobacilli. This is available in a capsule called Bacid®.

The present report covers the following groups: antibiotic diarrhea, infectious diarrhea, colostomies with either diarrhea or constipation, constipation from certain drugs, mucous or spastic diarrhea, diverticulitis, ulcerative colitis, abnormal fermentation, and several cases following treatment of amebiasis.

Results

A total of 59 patients with various abdominal symptoms with and without diarrhea were studied (Table I). There were 4 cases of constipation, two in colostomies and 2 as a result of drugs; these were well controlled with Bacid. A breakdown of the cases is as follows: There were 22 antibiotic diarrheas, many of which were resistant to anticholinergics, opium, kaolin, etc. Results with Bacid were extraordinarily rapid and nearly all of them good. There was 1 case of diverticulitis, one of pancreatitis, one of mucus colitis, two of ulcerative colitis which had been resistant to many other agents, one each of idiopathic

TABLE I

(0—no effect. +—little effect. ++—good effect. +++—abolished symptoms.)

Case	Patient	Sex	Age	Presenting symptoms, diagnosis, and previous therapy	Response to Bacid	Evaluation
1.	S. d. C.	M	62	Gas, cramps, foul odor of gas and stools; 6-10 stools p.d. Yeasts and undigested food in stools, physical examination negative. Diverticulitis.	12 caps. p.d. Improved considerably, but relapsed when he did not take Bacid.	++
2.	A. V.	F	36	Antibiotic diarrhea following hysterectomy and cystitis, treated with Chloromycetin. Diarrhea resembling hyperactive bowels, loud rumbling.	2 caps. q.i.d. stopped diarrhea and distress within 24 hours; no recurrence.	+++
3.	H. S.	F	58	Chronic pancreatitis, explosive diarrhea with foul stools, frequent abdominal cramps and pain.	2 caps. t.i.d. did not help.	0
4.	M. E.	F	57	Chronic salmonella infection, protracted cramps and diarrhea, urinary infection. Chloromycetin and Furadantin abolished infection, but diarrhea continued (antibiotic diarrhea).	2 caps. 5 x p.d. Diarrhea stopped in 24 hours, no recurrence.	+++
5.	N. S.	M	48	Following visit to Mexico, diarrhea and fever. No organisms found in stool. Declomycin brought fever down, slowed b.m.'s to 3-4 p.d., but painful cramps persisted, patient extremely weak, fainted.	12 caps. p.d. Diarrhea and cramps stopped in 6 hrs., no recurrence.	+++
6.	F. B.	M	60	In 1948, colostomy for lymphogranuloma inguinale. Since then, frequent bouts of foul smelling diarrhea. No organisms found in stool.	2 caps. every 2 hrs. stopped bout of diarrhea within 6 hrs.; from then on, no more diarrhea, stools formed, with fruity odor. No recurrence.	+++
7.	M. G.	M	70	In 1953, colostomy for carcinoma of colon; in 1959, reoperated and obstructing bands and adhesions severed; treated with achromycin. Antibiotic diarrhea, no organisms found; cramps, weak, disoriented.	2 caps. q.i.d., diarrhea and cramps stopped within 8 hrs.; no recurrence.	+++
8.	N. S.	M	43	Large volumes of foul stools and gas, distention, no organism found, epidemic diarrhea; his baby had same type of diarrhea, was treated with antibiotics followed by persistent diarrhea.	2 caps. every 3 hrs., relief within 24 hrs.; recurred when medication was interrupted.	+++
9.	Ch. B.	M	46	Took Declomycin for upper respiratory infection, followed by abdominal cramps and diarrhea (up to	3 x 2 caps., complete relief, no recurrence.	+++

				same type of diarrhea, was treated with antibiotics followed by persistent diarrhea.	interrupted.	
9.	Ch. B.	M	46	Took Declomycin for upper respiratory infection, followed by abdominal cramps and diarrhea (up to 10 b.m.'s p.d.), prostration; antibiotic diarrhea.	3 x 2 caps., complete relief, no recurrence.	+++
10.	M. C.	F	21	Strep. throat treated with Tetrex, followed by violent abdominal cramps and diarrhea, antibiotic diarrhea.	2 caps. every 2 hrs. brought complete relief in 12 hrs., no recurrence.	+++
11.	A. S.	F	20	Cystitis treated with Chloromycetin, antibiotic diarrhea with cramps and frequent watery b.m.'s (20 p.d.).	2 caps. every 2 hrs. terminated condition in 12 hrs.	+++
12.	P. W.	F	40	Resection of colon for carcinoma, colostomy. Chronic constipation. Laxatives and regulation of diet helped little, often followed by secondary constipation.	3 x 3 caps. p.d. good emptying of soft stools from colostomy within 24 hrs. and since then well on continued therapy.	+++
13.-16.	X.	M	10-14	4 boys with upper respiratory infection treated with Achromycin (2), Ilosone (1) and Declomycin (1). Violent diarrhea and cramps, up to 20 b.m.'s p.d., antibiotic diarrhea.	4 x 2 caps. p.d. stopped diarrhea and cramps within 24 hrs. No recurrence.	+++
17.	A. B.	F	48	Spastic colon for last 20 years; presently rather acute diarrhea, + 10 b.m.'s p.d., cramps, desperate. No specific organisms in stool. Kaopectin-belladonna helped only little, but was continued.	1 cap. t.i.d., within 1 week diarrhea and cramps disappeared, slight constipation, no discomfort; no recurrence.	+++
18.	T. D.	M	64	Severe diarrhea, malodorous stools for 1 week, no fever, asthma; took prednisone. Echo virus epidemic.	2 caps. every 2 hrs. Completely relieved in 12-24 hrs. no recurrence.	+++
19.	C. D.	F	26	Upper respiratory infection, erythromycin, severe diarrhea, cramps, rectal itching and excoriation. Antibiotic diarrhea.	2 caps. every 2 hrs. Completely relieved in 24 hrs.; no recurrence.	+++
20.	F. P.	F	60	Upper respiratory infection treated with Declomycin. Mild diarrhea, severe rectal itching. Antibiotic diarrhea.	2 caps. every 2 hrs. Completely relieved in 24 hrs., but relapsed when Bacid was stopped.	++
21.	M. J.	F	72	Osteoarthritis and spastic colon; takes codeine regularly and is badly constipated, has to take enemas and cathartics.	2 caps. every 2 hrs. (12 p.d.). Normal stools in 24-36 hours, but recurs within 1 week when Bacid is omitted.	++
22.	A. G.	M	36	Recurrent hepatitis (had infectious hepatitis 6 yrs. ago) with upper respiratory infection. Fever, increased bilirubin (1.7 mg.%), prostrate, anorexic. Declomycin. Antibiotic diarrhea?	2 caps. every 2 hrs. Diarrhea and malaise stopped completely. No recurrence.	+++

TABLE I *(Continued)*

(0—no effect. +—little effect. ++—good effect. +++—abolished symptoms.)

Case	Patient	Sex	Age	Presenting symptoms, diagnosis, and previous therapy	Response to Bacid	Evaluation
23.	L. S.	F	45	Mucus spastic colon, no frequency (2 b.m.'s p.d.). Painful rectal spasms.	2 caps. every 2 hrs. completely o.k. 24 hrs. No recurrence.	+++
24.	D. B.	M	24	Antibiotic diarrhea, resistant to anticholinergic drugs and opium.	2 caps. every 2 hrs., diarrhea and cramps stopped within 24 hrs., no recurrence.	+++
25.	J. L.	M	60	Loose stools, rectal burning; stools negative for ova, parasites, pathogenic bacteria, or protozoa. Diverticulitis (X-ray).	2 caps. 6 x p.d. for 5 days, no symptoms 24 hrs. later. Then, 1 cap. t.i.d. Symptoms recur when he stops Bacid.	++
26.	E. B.	F	46	Right upper lobe pneumonia following ureterotomy treated with Cosa-Tetrastatin. Severe antibiotic diarrhea and cramps.	2 caps. t.i.d. stopped diarrhea in 24 hrs., Bacid continued for 1 week, no recurrence.	+++
27.	H. S.	M	47	Chronic idiopathic ulcerative colitis, treated with prednisone, Neobacin, opium, with no results.	2 caps. t.i.d. and Diodoquin 2 tabl. b.i.d., controlled diarrhea in less than 3 days. One week later, Diodoquin was stopped, only on Bacid caps. b.i.d. Excellent results for last 3 months.	+++
28.	J. S.	M	27	Chronic amebiasis, constipation. Carbarsone was followed by cramps and severe diarrhea.	2 caps. t.i.d. stopped diarrhea in 48 hrs., but patient became "gassy" and stopped Bacid, no recurrence.	++
29.	L. G.	M	51	Severe sinusitis treated with Panalba. He had been treated with Panalba before, and every time a severe antibiotic diarrhea had followed.	2 caps. t.i.d., no diarrhea to Panalba.	++
30.	B. S.	F	70	Idiopathic diarrhea for 1 month, no pathogenic organisms found in stool, proctoscopy and x-ray negative. Treated for weeks without result with Cremomycin, Donnagel with Neomycin, bismuth subcarbonate, Pro-Banthine, paregoric.	2 caps. b.i.d., with 10 gm. Diodoquin. Cured in 3 days, continued on Bacid, excellent result, no recurrence.	+++
31.	M. C.	F	47	2 yrs. history of purulent idiopathic ulcerative colitis with rectal abscess. Proctoscopy and x-ray positive for ulcerative colitis. No results of therapy with vitamins, testosterone, Aralen, antibiotics.	Neobacin and Bacid, 2 caps. b.i.d. Diarrhea stopped in 3 days, gained 8 lbs. in 25 days; Bacid 1 cap. b.i.d. for 1 week, then stopped. Excellent results now for last 3 months.	+++
32.	I. B.	F	54	Carcinoma of sigmoid colon resected 2 yrs. ago;	2 caps. t.i.d. produced liquid stools; Bacid reduced to 1 cap. b.i.d., produces 1 semi-	++

				Vitamins, testosterone, Aralen, antibiotics.	then stopped. Excellent results now for last 3 months.	
32.	I. B.	F	54	Carcinoma of sigmoid colon resected 2 yrs. ago; colostomy. Now recurrence of carcinoma and spread in abdomen. Always had difficulty with constipation and had to take enema into colostomy.	2 caps. t.i.d. produced liquid stools; Bacid reduced to 1 cap. b.i.d., produces 1 semi-solid stool in morning.	++
33.	L. L.	M	58	Acute diarrhea, abdominal pain, 2 days, epidemic diarrhea.	Bacid, 12 caps. p.d. Diarrhea and pain gone in 12 hrs. Took Bacid for 3 days, no recurrence.	+++
34.	F. L.	M	55	Wife of L. L., same symptoms.	Took Bacid for 2 days only; diarrhea and pain gone in 12 hrs., so she stopped next day; recurrence, took Bacid for 5 days, diarrhea and pain gone in 12 hrs., no recurrence.	+++
35.	J. K.	M	24	Ate spoiled fish, food poisoning, tenesmus, diarrhea, fever, abdominal pain, put on Kaopectin and anti-cholinergic drug, symptoms gone in 5 hrs., but recurred in 12 hrs.	12 p.d. All symptoms gone in 12 hrs. Took Bacid for 3 days, no recurrence.	+++
36.	M. D.	F	32	Epidemic diarrhea with fever, abdominal pain.	Took Bacid for 4 more days, no recurrence.	+++
37.	S. P.	M	24	Epidemic diarrhea, fever, cramps. Lactinex 12 tabl. p.d., only fair results.	12 p.d., relief overnight, Bacid 3 days, no recurrence.	+++
38.	G. F.	F	55	Epidemic diarrhea, no fever, severe abdominal pain and cramps, foul smelling stools.	12 p.d., controlled overnight, no recurrence.	+++
39.	M. A.	F	24	Cystitis and occasional diarrhea, constant abdominal discomfort and rumbling. Stools negative for pathogenic organisms. Cystitis treated with antibiotics, fever disappeared, but postantibiotic troublesome diarrhea developed.	8 caps. for 48 hours abolished abdominal symptoms; continued Bacid for 3 days, no recurrence.	+++
40.	C. M.	F	55	Food poisoning from sea food. Vomiting, diarrhea, severe abdominal cramps.	1 cap. every 2 hrs.; in 4 hrs., all symptoms disappeared. Continued Bacid 4 caps. p.d. for 3 days. No recurrence.	+++
41.	B. B.	M	26	Epidemic diarrhea for last 48 hrs. Severe cramps, tenesmus, red blood on stools.	Bacid 8 caps. p.d. for 3 days, 6 caps. for 2 days. Improved in 6 hrs., no recurrence.	+++

TABLE I *(continued)*

(0–no effect. +–little effect. ++–good effect. +++–abolished symptoms.)

Case	Patient	Sex	Age	Presenting symptoms, diagnosis, and previous therapy	Response to Bacid	Evaluation
42.	J. R.	F	45	Epidemic diarrhea for 48 hrs. Vomiting, diarrhea, tenesmus and severe rectal bleeding from hemorrhoids.	2 caps. q.i.d. at 4 p.m. Improved shortly and all symptoms gone next morning. No recurrence.	+++
43.	M. D.	F	40	Epidemic diarrhea for 24 hrs., 101° fever, severe diarrhea.	2 caps. q.i.d. Symptoms gone in 8 hrs., fever in 24 hrs. No recurrence.	+++
44.	M. V.	F	32	Antibiotic diarrhea following Terramycin postoperatively for urinary tract infection. Severe diarrhea, gas, rumbling for 12 hrs.	2 caps. q.i.d. Symptoms diminish progressively and are gone in 6 hrs. No recurrence.	+++
45.	M. A.	F	26	See also under patient No. 39. Antibiotic diarrhea and fever had disappeared under administration of Bacid. However, 1 week later fever of 101°C. recurred. Sulfathalidine 6 gm. p.d. did not affect fever. Cultures of stool–no pathogenic organisms. Complete gastrointestinal x-ray showed only hyperactive bowel and gas; 3 proctoscopies negative.	2 caps. q.i.d. Fever and bowel hyperactivity gone in 24 hrs. Question of early ulcerative colitis which may have responded favorably to Bacid.	+++
46.	D. D.	M	26	Chronic gastrointestinal cramps and foul smelling flatus for years; chronic abnormal intestinal fermentation? Belladonna with phenobarbital and kaopectate had only fair effects.	2 caps. q.i.d. for 2 days, then 1 cap. q.i.d. abolished symptoms in 24 hrs. Patient is being kept on the latter dose of Bacid, because symptoms recurred within 1 week after Bacid was stopped.	++
47.	M. H.	M	62	Epidemic profuse diarrhea 48 hrs., cramps, gas.	4 caps. q.i.d., relieved within a few hrs.; on Bacid for 3 days, no recurrence.	+++
48.	L. H.	F	60	Wife of M. H., No. 47; very neurotic. Same symptoms as husband for 48 hrs.	2 caps. q.i.d. controlled diarrhea and gas, but not cramps; the latter controlled with belladonna-phenobarbital. Symptoms recurred after these drugs were stopped, but Kaopectate-neomycin controlled symptoms.	+
49.	N. S.	M	45	Diarrhea for 3 days, stool cultures negative, gastrointestinal x-ray: duodenal ulcer. Epidemic diarrhea?	2 caps. q.i.d. diminished diarrhea to 2 b.m.'s p.d. for 1½ weeks.	+
50.	M. C.	F	21	Epidemic diarrhea, pain, cramps, gas for 24 hrs.	2 caps. q.i.d. for 1 day, then 1 cap. q.i.d. for 3 days. All symptoms gone in 4 hrs.,	+++

[illegible]	N. S.	M	45	Diarrhea for 3 days, stool cultures negative, gastrointestinal x-ray: duodenal ulcer. Epidemic diarrhea?	2 caps. q.i.d. diminished diarrhea to 2 b.m.'s p.d. for 1½ weeks.	+
50.	M. C.	F	21	Epidemic diarrhea, pain, cramps, gas for 24 hrs.	2 caps. q.i.d. for 1 day, then 1 cap. q.i.d. for 3 days. All symptoms gone in 4 hrs., no recurrence	+++
51.	M. D.	F	28	Epidemic diarrhea, vomiting, pain, cramps, gas for about 24 hrs.	1 tablet Donnatal stopped vomiting, but not diarrhea. Bacid, 2 caps. q.i.d. stopped diarrhea in 4 hrs., no recurrence.	+++
52.	L. S.	M	26	Foul smelling flatus and rectal itch for 6 months. Chronic abnormal intestinal putrefaction?	2 caps. q.i.d. stopped symptoms in 24 hrs., no recurrence.	+++
53.	D. A.	F	35	Severe vomiting and diarrhea, syncope and collapse. Epidemic diarrhea.	Compazine injection stopped vomiting, but not diarrhea. Bacid 2 caps. q.i.d. for 4 days. Felt better within few hours, symptoms gone in 12 hrs. No recurrence.	+++
54.	K. B.	F	59	Lymphogranuloma inguinale contracted 30 yrs. ago; almost complete occlusion of rectum, colostomy. Lately, colostomy closed up and was repaired 1 month ago; since then frequent uncontrolled diarrhea from colostomy.	Anticholinergic drugs and Bacid had no effect.	0
55.	R. S.	F	60	Patient had repeated episodes of infections that were treated with Chloromycetin; each time, administration of the antibiotic was followed by explosive diarrhea with gas, cramps, tenesmus, and abdominal pain, which persisted for one week after Chloromycetin administration had been stopped.	For this reason, when antibiotic therapy was necessary again, each dose of Chloromycetin was given with 2 caps. of Bacid. No diarrhea or other complaints occurred during 2 such courses; no recurrence.	+++
56.	H. W.	F	64	Epidemic diarrhea with nausea and vomiting for 8 hrs.	2 caps. every 4 hrs. After 4 doses of Bacid diarrhea, nausea, vomiting, stopped. However on the 3rd day, large amounts of gas, which disappeared when Bacid was stopped. No recurrence.	++
57.	C. H.	F	63	Following administration of Inversine for hypertension, patient began to suffer from constipation with very malodorous gas.	2 caps. q.i.d. for 1 day, then 2 caps. t.i.d. All complaints gone after 24 hrs., no recurrence.	+++
58.	A. R.	F	55	Epidemic diarrhea for 6 hrs., with violent cramps, gas, tenesmus, subnormal temperature; very sick, dizzy, weak.	2 caps. q.i.d. Well within 24 hrs., no recurrence.	+++
59.	Mc. C.	M	24	Son-in-law of No. 58, A. R.	Same symptoms and course as mother-in-law; obtained Bacid from her.	+++

and carbarsone diarrhea, and 5 of the most interesting were colostomies with foul diarrhea.

In most cases there was a rapid improvement in less than 24 hours. Four cases recurred when Bacid was stopped too early. In the cases labeled epidemic or virus diarrhea, a great number of stools were cultured, but no pathogenic bacteria were found. As can be seen from Table I, there were only a few failures, namely in one case of chronic pancreatitis with explosive diarrhea and a colostomy with diarrhea.

Summary and Conclusions

Bacid, a capsule form of a dried viable culture of lactobacillus acidophilus, was used in the treatment of 59 cases with diarrhea of various etiologies, and cases with constipation, abnormal fermentation, food poisoning, etc. In 22 cases with antibiotic diarrhea, 20 excellent and 2 good therapeutic results were obtained. In 19 cases of epidemic diarrhea, excellent results were obtained in 17 cases, and fair results in 2 cases. Therapeutic failures occurred in 1 case of chronic pancreatitis with diarrhea, and in one case of colostomy with diarrhea. The results in this series are as shown in the table. It is suggested that this technic merits further serious study.

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President's Message

Because I have been attending the various Regional Meetings, it was not possible to prepare a message for the last issue.

I want to take this means of publicly thanking all those who were responsible for the success of the two Regional Meetings already held and, I am sure that the next one in Milwaukee will be equally as good. Much has been learned both medically and administratively from these sessions.

The papers presented by the speakers were excellent and we hope to have most of them for publication in the near future.

These Regional Meetings serve a very important purpose in an organization which is as large as the American College of Gastroenterology and which has a membership throughout the country. I sincerely hope that they will be continued in future years and in other cities, thus giving all of our members an opportunity to participate and to attend at least one meeting of the organization each year.

Our Cleveland program committee, under the Chairmanship of Dr. Robert R. Bartunek, is planning several new types of sessions which should prove to be a welcome change from the general run of medical meetings. It is not too early to start making your hotel reservations for October and cards are being mailed to the membership with the next issue of the College Bulletin. Nonmembers are invited to attend the 27th Annual Convention and they may obtain hotel reservations by contacting our Executive Director.

Henry Baker

NEWS NOTES

1961 Ames Award Contest of The American College of Gastroenterology

The American College of Gastroenterology, in cooperation with the Ames Co. of Elkhart, Ind., again takes pleasure in announcing the 1961 Ames Awards Contest for the best papers on gastroenterology or an allied field, published in The American Journal of Gastroenterology between July 1960 and June 1961.

The first prize will be $500.00; the second prize will be $300.00 and the third prize will be $200.00.

The selection of the winning papers will be made by the Research Committee of the American College of Gastroenterology and the awards will be presented at the Annual Banquet of the College in Cleveland, Ohio, in October of 1961.

The decision of the judges will be final.

In Memoriam

We record with profound sorrow the passing of Dr. Jose Alvarez Aguilar, Mexico D.F., Fellow of the American College of Gastroenterology. We extend our deepest sympathy to the bereaved family.

ABSTRACTS FOR GASTROENTEROLOGISTS

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GASTROINTESTINAL TRACT

ASSOCIATION OF GASTRODUODENAL LESIONS WITH MENIERE'S SYNDROME: Roger Wyburn-Mason. Brit. M. J. 5114:79 (10 Jan.), 1959.

That there is some nervous connection by which labrynthian stimulation causes disturbance of gastric and duodenal function is testified to by the experience of Wolf (1946) in which he demonstrated, via balloon and barium technic, that irrigation of the external ear with cold water produced disturbance of motor activity of the first portion of the duodenum. This impairment of function never took place in the absence of nausea, and vice versa.

Clinically, it has been observed that irritation of the stomach and duodenum by toxins or other agents, or by gross distention, often produces symptoms of labrynthian disturbance as nausea, vertigo, tiinnitus, sweating, syncopy, and vasomotor changes.

Five cases are presented which indicate the association of Meniere's syndrome with such gastroduodenal lesions as paraesophageal hernias, duodenal ulcers, diverticula, and pyloric stenosis. The symptomatology of Meniere's syndrome was improved with the treatment of the associated gastroduodenal lesions and was made worse with the exacerbation of these conditions. In all these instances the tests for vestibular and cochlear functions were abnormal.

The theoretical basis for this relationship is fully discussed.

EZRA J. EPSTEIN

ESOPHAGUS

ENDOSCOPY: Edward B. Benedict. New England J. Med. 260:478 (5 Mar.), 1959.

The author reports on medical progress of endoscopy since 1955. Bergmann and Charnas report on tracheobronchial rests in the esophagus and their relation to benign strictures and certain types of carcinoma, such as the oat-cell type.

Dr. Benedict quotes Eddy Palmer's experience with the vigorous approach to gastrointestinal hemorrhage in 228 patients. He recommends early esophagoscopy and gastroscopy following ice-water lavage of the stomach. This was followed at once by manipulative x-ray studies of the gastrointestinal tract. The bleeding was identified within a few hours after admission in 89 per cent of the cases. The most common lesions responsible for the bleeding were esophageal varices (36 cases), erosive esophagitis (19 cases), hiatus hernia (14 cases) and erosive gastritis (33 cases). Although 102 patients had duodenal ulcer, hemorrhage could be attributed to only 55

(23 per cent). Emergency surgery was performed in 48 cases (20 per cent) with an 8 per cent operative mortality, 3 per cent from exsanguination.

Smythe et al performed emergency esophagoscopy in 24 cases with no complications or reactivation of bleeding.

Cases of heterotopic (Barrett type) of epithelium in the gastric lining at the terminal esophagus, responsible for discreet ulcerations in association with hiatus hernia, were reported by Wolf, Som and Marshak.

Stewart et al found a sliding hiatus hernia in 42 out of 66 patients whom they had treated for reflux and peptic esophagitis.

Hodges and Rubin having studied inflammatory lesions of the esophagus and stomach by x-ray concede the failure to demonstrate lesions seen by endoscopy.

SAUL A. SCHWARTZ

STOMACH

POSTGASTRECTOMY PANCREATIC SECRETION (GLYCINE ADMINISTRATION TO PATIENTS WITH POSTGASTRECTOMY SYNDROME): Yoshio Akiya, Minoru Hirota, Munetoshi Uchida, Hidemichi Goto and Takehiko Matsuhashi. Yokohama M. Bull. 10:140 (June), 1959.

Different types of therapy have been used to relieve distress following gastrectomy.

This paper deals with the so-called "dumping syndrome" and early and late symptoms of the postgastrectomy syndrome. Twenty-two cases of gastrectomized patients are reported being treated with glycine. Methods of administration and dosage are discussed. Tables are shown giving patients' symptoms and results after therapy. Side reactions on the use of this drug is also given.

ABRAHAM BERNSTEIN

SERIOUS COMPLICATIONS OF PEPTIC ULCER AFTER ACUTE MYOCARDIAL INFARCTION: Joseph C. Shipp, Victor W. Sidel, Robert M. Donaldson, Jr. and Seymour J. Gray. New England J. Med. 261:222 (30 July), 1959.

It is not uncommon to see stress situations activate or initiate peptic ulcer. Myocardial infarction, no doubt, is a stress state and hence may also result in peptic ulceration. Complications of peptic ulcer, such as hemorrhage and perforation during myocardial infarction take on added significance. Six cases are reported—four with perforation and two with hemorrhage during acute myocardial infarction. The authors studied the excretion of uropepsin and adrenocortical steroids durig the acute and convalescent phase of 20 patients with coronary heart disease. Four of the 10 patients with acute myocardial disease showed an increase in the uropepsin excretion on admission and became normal during convalescence. Among the 10 controls none showed increased uropepsin excretion on admission. The urinary 17-hydroxycorticoids and the 17-ketosteroids did not differ significantly in the two groups. Shock or anemia associated with peptic ulcer may precipitate myocardial infarction in susceptible persons. Peptic ulcer disease as a complication of myocardial infarction is not too widely recognized. Prevention of this complication is important in all patients with myocardial infarction with previous history of peptic ulcer disease. Food should not be withheld and anticoagulant therapy if used, should be with extreme caution. Complications of peptic ulcer disease in patients with myocardial infarction are extremely hazardous.

A. J. BRENNER

A SURVEY OF DUODENAL ULCER (724 CASES): D. L. Kippen. Canad. M. A. J. 81:91 (15 July), 1959.

The author reviews 724 cases of duodenal ulcer studied between 1952 and 1954 at Winnipeg Clinic. This study gives special attention to such characteristics as the nature, frequency, severity of symptoms in the incidence of ulcer complications, the response to medical treatment, and the need for ulcer surgery. Cases were included in

the survey if positive radiologic or pathological evidence of duodenal ulcer was available.

Medical treatment seemed to vary as to the severity of the symptoms and in only 12 per cent was the "ideal program" carried out. The attending doctor usually outlined a program of treatment considered suitable to the patient with regard to both the duration and severity of his symptoms and willingness and ability to carry it out.

As to benefit of anticholinergic drugs in the therapy, it was concluded that as a supplement to the usual therapy, they were of little value.

L. K. BEASLEY

INTESTINES

APPENDICITIS AFTER APPENDECTOMY: Bernard Sigel and M. W. Wolcott. J.A.M.A. 170:1151 (4 July), 1959.

Three cases of acute appendicitis occurring after previous appendectomy, done as a prophylactic procedure during the course of other surgery, are reported. Based on this series, the authors assume that appendectomy should not be done as part of another procedure unless ideal exposure of the appendix is possible. A valid warning that history of appendectomy does not rule out appendicitis is given.

BERNARD FARFEL

MALABSORPTION SYNDROME FOLLOWING EXTENSIVE RESECTION OF THE SMALL INTESTINE: W. I. Morse, R. C. Dickson, E. P. Nonamaker and G. H. Embree. Canad. M. A. J. 81:88 (15 July), 1959.

This is an additional report of another instance where a patient has survived after a complete resection of the small intestine distal to the proximal three feet of jejunum. Trauma necessitated this operation which consisted of a jejunocolic anastomosis. As a result of this, two blind pouches were created soon after the initial operation. A severe malabsorption syndrome followed.

Some seven months after the initial operation, the jejunocolic anastomosis was replaced eliminating the blind pouches by anastomosing the distal end of the remaining jejunum to the cecum thus exposing the intestinal content to the entire colon. Very soon after this second procedure, the patient began to show improvement. In fact, his diarrhea was reduced to two stools daily and he was capable of returning to lighter forms of manual labor.

L. K. BEASLEY

PANCREAS

HYPERPARATHYROIDISM AND PANCREATITIS: REPORT OF A CASE: Mortimer J. Lacher, Jack A. Goldberg, Don F. Thomas and George L. Calvy. New England J. Med. 261:239 (30 July), 1959.

This is a case presentation of acute intermittent pancreatitis in a proven case of hyperparathyroidism. Which came first is questionable. The associations of the two diseases is not uncommon. The authors state that even in the absence of the classic complications of hyperparathyroidism, the presence of hypercalcemia (13.6 mg. per cent in this case), hypophosphatemia (serum phosphorus of 2.3 mg. per cent in this case), and hypercalciuria (420 mg. excreted in 24 hours in this case), constitute sufficient reason to explore the neck and mediastinum, if necessary, in search for a parathyroid adenoma. The percentage tubular reabsorption of phosphorus and the phosphorus clearance determination, may help diagnostically before surgery. (Average tubular reabsorption in this case was 70.13 and average phosphorus clearance was 27.5 in two determinations of each). Finally the authors suggest that recurrent pancreatitis may serve as an early clue to the presence of hyperparathyroidism.

A. J. BRENNER

PATHOLOGY AND LABORATORY RESEARCH

EXPERIMENTAL SHIGELLOSIS IN MICE. I. CHRONIC INFECTION WITH SHIGELLA DYSENTERIAE TYPE 2: G. N. Cooper. Australian J. Exper. Biol. & M. Sc. 37:193 (June), 1959.

With the exception of cholera, few if any of the enteric diseases of man may be reproduced in experimental animals by oral administration of bacteria. However, such method of intestinal infection can be achieved if the feeding of Shigella or Salmonella organisms is preceded by oral streptomycin. This substance kills the normal intestinal flora especially the colon bacilli which interfere with the implantation of the pathogenic bacilli. The latter must be streptomycin resistant strains in order to produce disease. Following the seeding of mice with 100 or less organisms these animals excreted large amounts of Shigella for a number of weeks in the feces. The feces were soft and increased in volume. There was, however, no diarrhea. Introduction of streptomycin resistant *Escherichia coli* into the gastrointestinal tract eliminated the Shigella organisms rapidly from the gastrointestinal tract. None of the animals died; however, they were sacrificed with coal gas inhalation and ulcerative lesions were found along the gastrointestinal tract particularly the appendix and the cecum. Microscopically there was a severe destruction of the mucosa similar to human Shigellosis. The presence of the normal bacterial flora prevented the invasion of the Shigella into the intestinal wall.

H. B. Eisenstadt

EXPERIMENTAL SHIGELLOSIS IN MICE. II. IMMUNOLOGICAL RESPONSES TO SHIGELLA DYSENTERIAE TYPE 2 INFECTION: G. N. Cooper and Jill A. Pillow. 37:201 (June), 1959.

The localized infection of the intestinal tract with Shigella organism in mice described in the first paper was associated with various immunological responses similar to those observed during human infection. There was a steady increase of specific serum agglutinins shown by the hemagglutination reaction. The maximum antibody titer in the serum appeared 14 days after the infection. In addition, specific coproantibodies were detected from the feces of the infective animals with the same hemagglutination method. They also occur in human infection. The maximum titer of the latter antibodies appeared one week after the infection. These substances seem to be released by the lymphocytes accumulated at the site of the infection.

H. B. Eisenstadt

CLINICAL STUDIES ON LIVER CATALASE ACTIVITY IN GASTRIC CARCINOMA CASES: II. EXPERIMENTAL SUPPLEMENT: Iwao Yamaguchi. Tohoku J. Exper. Med. 70:305 (25 Sept.), 1959.

Following the clinical observations reported in his first paper, the author tested the aqueous extract of gastric carcinoma tissue for its inhibitory effect on the catalase activity of the mouse liver. The author's object was to study the relation of this effect to the nature of the tumor on the one hand and to the liver catalase activity of the patient on the other.

Aqueous extracts from 39 gastric carcinoma tissues were injected into the peritoneum of mice whose liver catalase activity then was measured. Liver catalase activity in these mice was found to be significantly lower than in control mice. Catalase lowering activity of the tumor extract was not dependent on the macroscopic or microscopic features of the tumor. Decreased liver catalase activity of gastric carcinoma cases had little relation to the catalase lowering activity of the tumor extract but showed close parallelism to the catalase depressing ability of the tumor itself.

Walter Cane

EMOTION AND GASTRIC ACTIVITY: C. T. Seymour and J. A. Weinberg. J.A.M.A. 171:1193 (31 Oct.), 1959.

A study of 24 men with duodenal ulcers was undertaken to demonstrate the gastrointestinal effects of emotional tension. Measurements of gastric acidity, motility and tonicity as response to psychological stimulation were made before and after vagotomy. The appearance postoperatively of overt signs of emotional stress similar to that elicited preoperatively was used as the criterion for a standard test procedure.

Although the patients reacted strongly to psychic stimulation, the results of the analyses revealed no gastric response in secretion, or activity after vagotomy, and all the ulcers showed healing.

EZRA J. EPSTEIN

CONTRIBUTIONS OF THE PATHOLOGIST TO PRESENT-DAY CONCEPTS OF GASTRIC ULCER: S. L. Robbins. J.A.M.A. 171:2053 (12 Dec.), 1959.

The author studied 243 patients with gastric ulcer at autopsy. The results obtained are weighted. The patients were over 50 years of age, many of the patients were terminal and were suffering from terminal malignancy; therefore it is not surprising that one-third of the total showed gastric malignancy. The following were investigated: 1. Age—from the ages of 50 to 80 and over, the proportion of benign to malignant remained the same. 2. Size—about 10 per cent of lesions over 4 cm. were benign; about 20 per cent of ulcers less than 2 cm. were malignant. If, instead of taking the figures for the group as a whole, ulcers of 4 cm. or more are considered, there were 20 benign ulcers encountered as against 33 malignant. 3. Location—in the pyloric region, almost 25 per cent were malignant, on the greater curvature 50 per cent were malignant, on the lesser curvature 33 per cent were malignant. The influence of location on malignancy has been somewhat overemphasized, in this group healed benign lesions may not have been included because of the age of the group. 4. With respect to transformation of a benign into a malignant lesion, the author felt that this took place in only less than 1 per cent of peptic ulcers.

SAMUEL L. IMMERMAN

THE EFFECT OF CORTISONE ON THE RELEASE OF GASTRIC ACID BY HISTAMINE: E. R. Trethewie. Australian J. Exper. Biol. & M. Sc. 37:573 (Dec.), 1959.

An attempt was made to determine if cortisone increases the stomach acid output following histamine. The pylorus and esophagus were ligated and the stomach catheterized in decerebrate cats. Two doses of histamine were given I.V., with or without Benadryl, or subcutaneously. Cortisone acetate or Solu-cortef were also given before the first or second injection of histamine. The effects of cortisone or histamine alone were also studied.

Moderate doses of histamine produce slightly greater outputs of acid in the gastric juice when cortisone is injected intravenously. When large doses of histamine are given after Benadryl, while the concentration of acid released with or without Solu-cortef is similar, nevertheless the volume of acid is greater and the output more prolonged. Subcutaneous histamine injections were associated also with slightly increased volumes of acid secreted in the presence of cortisone but of similar duration. Cortisone did not influence (immediately) the concentration of gastric acid secreted. It is suggested that the inimical effect of cortisone in peptic ulcer patients may be due to inhibition of substances associated with healing rather than an effect on acid secretion.

ERNEST LEHMAN

EVALUATION OF DIAGNOSTIC PROCEDURES IN ONE HUNDRED PATIENTS WITH GASTROINTESTINAL SYMPTOMS: William B. Hunt, Jr., David Cayer and Zelma A. Kalnins. North Carolina M. J. 20:501 (Dec.), 1959.

Utilizing the saline gastric lavage technic, exfoliative cytologic studies were performed on 100 patients with gastrointestinal symptoms.

In general, a high index of suspicious cells were obtained in those patients who had malignant disease present. Exceptions to this were two cases of nonulcerating submucosal gastric lymphomas and one case of submucosal gastric cancer.

In two cases following resection for gastric carcinoma subsequent cytologic examination indicated recurrences, so that the authors feel that exfoliative cytology may be useful in following patients for possible future disease.

THEODORE COHEN

PSYCHOSOMATIC MEDICINE

HYPNOSIS IN THE TERMINATION OF HICCUPS UNRESPONSIVE TO CONVENTIONAL TREATMENT: A.M.A. Arch. Int. Med. 104:417 (Sept.), 1959.

The case of a 50-year old male is described who developed intractable hiccups 20 days after myocardial infarction. This resulted in complete exhaustion. Tongue traction, breathing into a paper bag, carbon dioxide inhalation from a tank, supraorbital pressure and other vagal maneuvers, thorazine, atropine, Benadryl and intravenous sodium amytal were without any effect on the hiccups. After 8 days of continuous singultus, hypnotic suggestion was used. After an hypnotic trance of 45 minutes the hiccups terminated. This showed that psychogenic factors play an important role in the etiology of hiccups. Hypnotic therapy should be tried in hiccups of any cause prior to phrenic nerve block and section.

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1. *British Medical Journal* 2:827, 1955
2. *American Journal of Gastroenterology* 28:439, 1957

BOOK REVIEWS FOR GASTROENTEROLOGISTS

RADIOLOGIC EXAMINATION OF THE SMALL INTESTINE, 2nd Edition: Ross Golden, M.D. Visiting Professor of Radiology, University of California, Los Angeles, Professor Emeritus of Radiology, Columbia University, Formerly, Director of Radiology, The Columbia-Presbyterian Medical Center, New York City, 560 pages, profusely illustrated, Charles C Thomas, Publishers, Springfield, Ill., 1959. Price $28.50.

Ross Golden needs no introduction to the medical profession. For many years he was chief of the Roentgenological Department of the Medical Center in New York City.

Within a period of several years, a smaller book on the study of the small intestines radiologically appeared from the pen of Dr. Golden. This former text received excellent reviews and now this enlarged and beautifully printed and illustrated volume with the newer physiology and pathology of the small intestine adds another milestone to our knowledge concerning the small bowel.

An extensive bibliography, name index and cross index completes the volume.

It is recommended to the internist, pediatricians and the radiologist as a most useful reference book.

RECENT ADVANCES IN PUBLIC HEALTH: J. L. Burns, M.D., D.Hy., D.P.H., Medical Officer of Health and Principal School Medical Officer, City of Salford, Lecturer in Public Health, University of Manchester. Second Edition, 370 pages, 54 illustrations, Little, Brown and Company, Boston, Mass., 1959. Price $10.00.

Physicians and laymen interested in or studying for a degree in public health will find valuable information in Dr. Burn's "Recent Advances in Public Health".

The references, important books, voluntary organizations, appendix, index of names and subject index, complete the text.

CIBA FOUNDATION STUDY GROUP #2—STERIC COURSE OF MICROBIOLOGICAL REACTIONS: In honor of Professor Dr. V. Prelog. Editors for the Ciba Foundation G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P. and Cecilia M. O'Connor, B.Sc., 115 pages, 37 illustrations, Little, Brown & Company, Boston, Mass., 1959.

Rather a complex and detailed discussion which the general practitioner will find difficult to follow. Numerous tables, graphs and equations, references and index complete the small book.

FUR LEBERKRANKE, EIN RATGEBER FUR DEN KRANKEN: Dr. Med. Habil. W. Bruhl, Korbach (Waldeck) with a foreword by Prof. Dr. Med. H. Kalk, Kassel, 75 pages, cardboard covers, illustrated, Georg Thieme Verlag, Stuttgart, 1960. Price $1.40.

It is customary in Germany for one of the physicians practicing in one of the Health Resorts or Spa, to write a concise pamphlet for the laity. In this instance, Dr. Bruhl's instructions are for those men and women who have liver and other biliary disturbances.

It is an instructive and well-written essay which undoubtedly will help the patient to better understand and to follow the instructions of his physician.

For the layman, the illustrations will be of aid in comprehending the text. Further, the author on page 50, outlines the diet and on page 59, the preparation of the various permissible meals.

A glossary and cross index are added features.

KLINISCHE PHYSIOLOGIE—Aktuelle Probleme in Ubersichten: Dr. W. A. Muller—Chefartzt der II Inneren Abteilung der Robert-Bosch-Krankenhauser, Stuttgart. Vol. I, 118 pages, paper covers, 42 illustrations, Georg Thieme Verlag, Stuttgart, 1960. Price $5.50.

Physicians, biochemists and experimental physiologists who read German, will be greatly interested in this clinical physiology.

The reviewer became interested in the E.E.G. description and its analysis, page 27, etc. It is clear and self-explanatory and worthwhile careful reading. Of further interest, is the section by Helmreich of Washington University School of Medicine, St. Louis, Mo., followed by an extensive bibliography. On page 87, the reader will find a most interesting article dealing with Phenyl-ketonuria as a possible cause of congenital mental retardation, and on page 89, the method for detecting the Phenylketone in the urine.

SEA WITHIN—THE STORY OF OUR BODY FLUIDS: William D. Snively, Jr., M.D., Lecturer in Pediatrics, University of Louisville School of Medicine, attending physician, Evansville Child Health Conferences, Medical Department, Mead Johnson Company, 150 pages, illustrated, J. B. Lippincott Company, Philadelphia, Pa., 1960.

Dr. Snively who is Vice President and Medical Director of Mead Johnson Company as well as lecturer in Pediatrics, University of Louisville School of Medicine, has given us a well written and concise book on the Story of Our Body Fluids.

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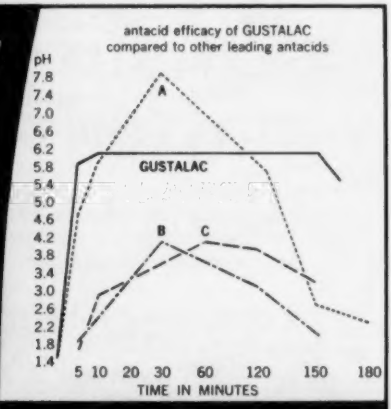

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1. Kirstner, J. B.: J.A.M.A. 166:1727, 1958.

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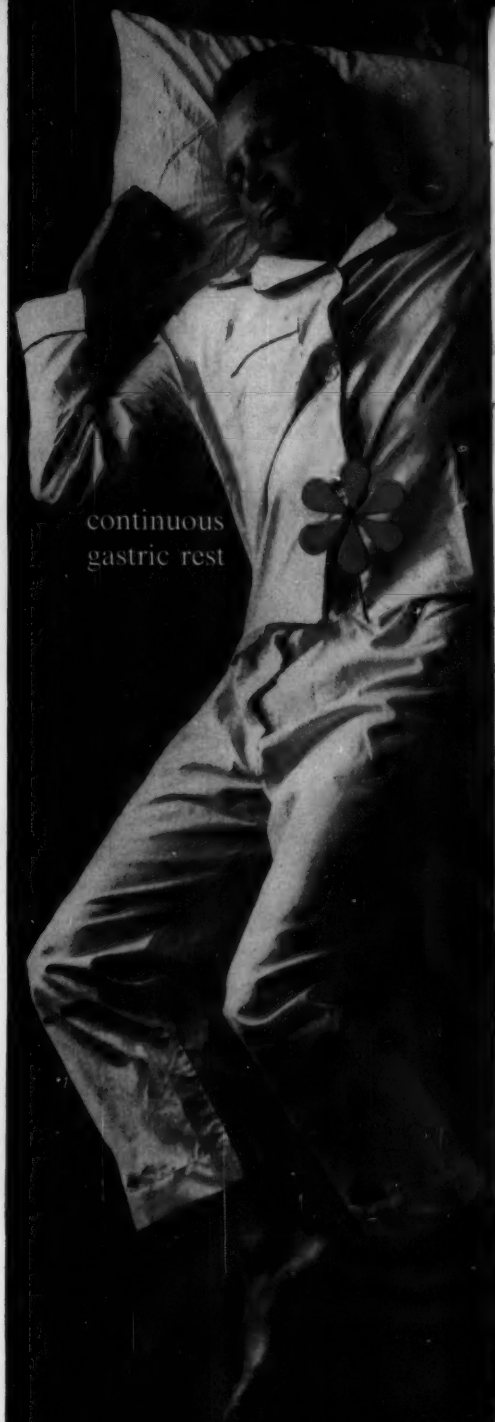

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"wearability"

NO TASTE FATIGUE
EXCELLENT RESULTS
NO CONSTIPATION

the most widely prescribed and most wearable of all antacids

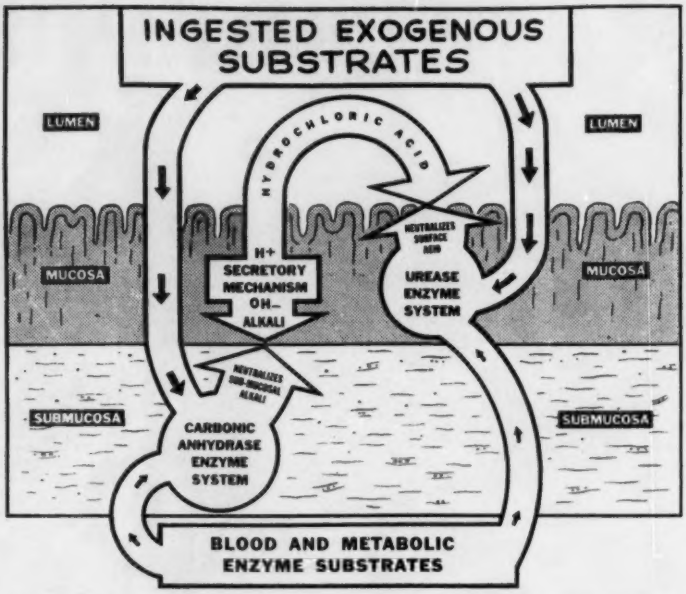
suspension tablets

Tablet Maalox No. 1 equivalent to 1 teaspoon Suspension
Tablet Maalox No. 2 equivalent to 2 teaspoons Suspension

A COMPLETE THERAPY FOR TREATMENT OF PEPTIC ULCER

CARBAMINE®

U.S. Pat. No. 2,840,506



Enzymic imbalance resulting from insufficient substrates may lead to peptic ulcer and other digestive disorders (full discussion in article by Goodfriend, Vanderkleed and Goodfriend). Carbamide has been designed to supply substrates for these enzyme systems, and thus aid in relieving symptoms, correcting acid-base equilibrium, aiding mucosal healing and normal digestion, and restoring homeostasis.(1)

The action of Carbamine medication as a direct approach to the elevation of the health status and resistance of gastrointestinal mucosa; its high degree of therapeutic effectiveness; and its complete absence of toxicity or side-effects indicates that it is an important contribution to the materia medica of peptic ulcer and certain other gastrointestinal diseases.(2)

FORMULA:
Carbamide with citric acid and sodium bicarbonate to produce sodium citrate and carbon dioxide when dissolved in water.

DOSAGE:
One packet T.I.D. after mealtime and one packet at bedtime.

REFERENCES:

(1) Goodfriend, Vanderkleed & Goodfriend. "Enzymatic Therapy of Peptic Ulcer and Digestive Disorders." American Journal Gastroenterology, Vol. 33, No. 1, Pgs. 80-89, January 1960.

(2) Kelly, H. T., M. D., "Treatment of Gastroduodenal Ulcer and Certain Digestive Disorders with Mucosal Enzyme Substances", American Journal of Gastro., Vol. 33, No. 12, December, 1960.

KEY PHARMACEUTICALS, INC., Miami 37, Florida

SPECIFIC ACTION...
FROM CARDIOSPASM TO RECTOSPASM

CAPSULES

DACTIL®

the only brand of piperidolate hydrochloride

FOR UPPER G.I. DISTRESS

- "unique" antispasmodic with powerful local anesthetic properties[1]
- "...specific for upper gastrointestinal pain and spasm..."[2]
- "...no toxic effects resulting from the clinical use of this compound have been reported."[1]

TABLETS

CANTIL®

the only brand of mepenzolate bromide

FOR THE COLON

- "...the most effective available colonic anticholinergic..."[3]
- "...provides selective action, confined principally to the lower G.I. tract."[4]
- "...singularly free of the side-effects commonly encountered with anticholinergics."[5]

DACTIL provides most rapid relief of gastrointestinal spasm, biliary spasm, cardiospasm, pylorospasm, spasm of biliary sphincter, biliary dyskinesia, gastric neurosis and irritability, postgastrectomy syndrome,and is useful as adjunctive therapy in selected inflammatory hypermotility states. DACTIL is almost entirely free of side effects but should be withheld in glaucoma.

Supplied: DACTIL (plain) 50 mg.; and DACTIL with Phenobarbital, 50 mg., with 16 mg. phenobarbital (may be habit forming). Bottles of 50.

LAKESIDE

CANTIL is highly effective in ulcerative colitis, irritable colon, mucous colitis, spastic colitis, diverticulitis, diverticulosis, malabsorption syndrome, rectospasm, diarrhea following G.I. surgery, bacillary and parasitic disorders.

The effect of CANTIL on the bladder is negligible, but caution should be observed in patients with prostatic hypertrophy. As with all anticholinergics, it should be withheld in glaucoma.

Supplied: CANTIL (plain) 25 mg.; and CANTIL with Phenobarbital, 25 mg., with 16 mg. of phenobarbital (may be habit forming). Bottles of 100 and 250.

References: (1) Rider, J. A.; Moeller, H. C., and Lee, J.: Am. J. Gastroenterol. *32*:714, 1959. (2) Modern Drug Encyclopedia and Therapeutic Index, ed. 6, New York, Drug Publications, Inc., 1955, p. 281. (3) Kleckner, M. S., Jr.: J. Louisiana M. Soc. *108*:359, 1956. (4) Kleckner, M. S., Jr.: Clin. Res. Proc. *5*:19, 1957. (5) Riese, J. A.: Am. J. Gastroenterol. *28*:541, 1957.

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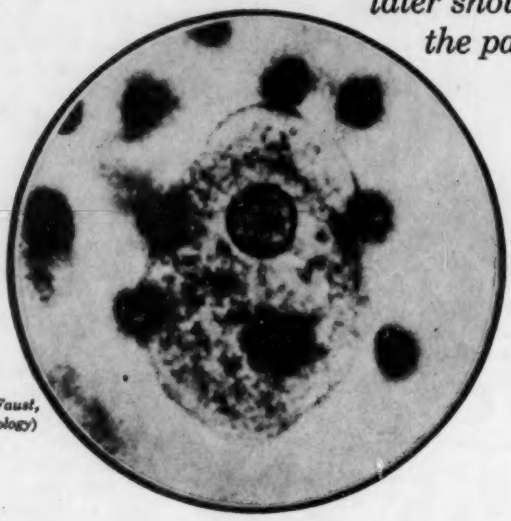
important new drug in the treatment of Amebiasis

90% cures with ANAMEBA®

Re-examinations four months later showed 90% of the patients were still cured.



(From Craig and Faust, Clinical Parasitology)

19% INCIDENCE: ANAMEBA SPECIFIC FOR AMEBIASIS

Frye and Lampert[1] recently studied the effect of Anameba in the treatment of asymptomatic Endameba histolytica carriers. They concluded that "Results of treatment . . . with Anameba in a group of 23 carriers of E. histolytica were excellent. No toxic reactions or side effects were noted among the 49 subjects who received the drug . . . There was no nausea, diarrhea or other sign of toxicity or side effects."

RESULTS OF POST-TREATMENT STOOL EXAMINATIONS FOR E. HISTOLYTICA

No. of Patients Examined	No. of Controls	No. Positive Before Treatment	No. Positive After First Course of Treatment
135	26	23	2

8 DAYS OF TREATMENT RESULTS IN 90% CURES

A single course of treatment (1 tablet t.i.d. for 8 days) results in improvement or complete alleviation of symptoms. Relief of symptoms of abdominal distress and flatulence is prompt. No toxic reactions or side effects occur, and no alteration in diet is necessary during Anameba therapy.

Each Anameba tablet contains: Iodochlorhydroxyquin 125 mg., and Bacitracin-methylene disalicylate 5000 U.S.P. Units. *Supplied:* In bottles of 24 tablets.

When you suspect amebiasis—specify ANAMEBA. For additional information, please write our Medical Department.

1. Frye, W.W., and Lampert, R.: Treatment of Asymptomatic Endamoeba histolytica Carriers with a Formulation of Bacitracin-Methylene Disalicylate and Iodochlorhydroxyquin (Anameba). Am. J. Gastroenterol. **34**:429-432 (Oct.), 1960.

CHICAGO PHARMACAL COMPANY
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DONNAGEL®

Donnatal® with Kaolin and Pectin compound

Robins

DONNAGEL's comprehensive antidiarrheal formulation gives the green light to normal activity, through its fast and dependable control of intestinal hypermotility.

Each 30 cc. (1 fl. oz.) of DONNAGEL contains:

Kaolin	6.0 Gm.	Natural belladonna alkaloids:	
Pectin	142.8 mg.	hyoscyamine sulfate	0.1037 mg.
Phenobarbital (¼ gr.)	16.2 mg.	atropine sulfate	0.0194 mg.
		hyoscine hydrobromide	0.0065 mg.

also available

DONNAGEL WITH NEOMYCIN • DONNAGEL-PG

DONNAGEL plus neomycin sulfate 300 mg. (as neomycin base 210 mg.) per 30 cc.

DONNAGEL plus powdered opium U.S.P. 24.0 mg. per fl. oz. (equivalent to paregoric 6 ml.). This is the usual adult dose.

All three forms available in bottles of 6 fl. oz.

NEW comprehensive digestant with the *most potent* enzyme available for digestion of

—also unsurpassed potency for digestion of starch, protein and cellulose

—the *only* digestant with Lipancreatin,* proven superior to Pancreatin N.F.

—the *only* digestant with fat-splitting lipase activity 12 times as great as that of Pancreatin N.F.

When the question is digestion because of your patient's inability to handle fat, starch, protein or cellulose, you can provide dependable relief with COTAZYM-B, which contains the essential pancreatic enzymes lipase, trypsin and amylase, plus bile salts and cellulase. A daily dose of 6 COTAZYM-B tablets is sufficient to emulsify and digest 50 Gm. of dietary fat, and to digest all of the protein and starch in a typical diet (100 Gm. protein, 250 Gm. starch) and 480 mg. cellulose.

Dosage: **1 or 2 tablets with water just before each meal.**

Supply: **Bottles of 48 tablets.**

Write for samples and comprehensive literature.

NEW Cotazym®-B

Lipancreatin Bile Salts Cellulase

ORGANON INC., West Orange, New Jersey

Organon

***The Significance of Lipancreatin (Pancreatic Enzymes Concentrated 'Organon')**

A product of original Organon research, lipancreatin provides *for the first time in digestant preparations a known, constant amount of fat-digesting lipase* in addition to trypsin and amylase. It surpasses in assayable digestive activity *all* presently available pancreatin preparations.

For the irritable G.I. tract

Milpath acts quickly to suppress hypermotility, hypersecretion, pain and spasm, and to allay anxiety and tension with minimal side effects.

AVAILABLE IN TWO POTENCIES

MILPATH-400—Yellow, scored tablets of 400 mg. Miltown (meprobamate) and 25 mg. tridihexethyl chloride.
Bottle of 50.

Dosage: 1 tablet t.i.d. at mealtime and 2 at bedtime.

MILPATH-200—Yellow, coated tablets of 200 mg. Miltown (meprobamate) and 25 mg. tridihexethyl chloride.
Bottle of 50.

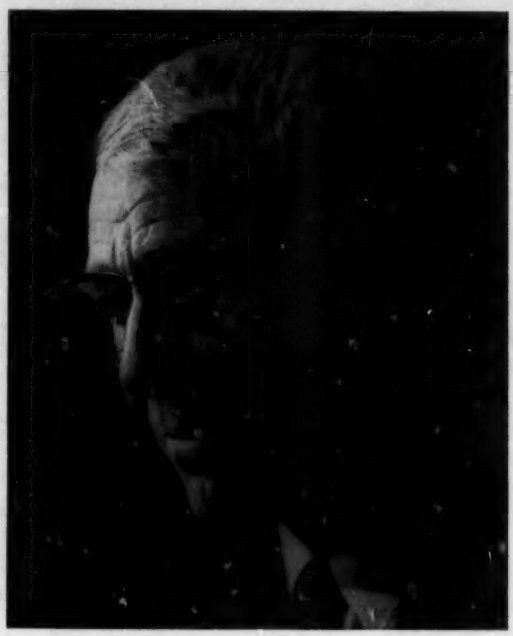
Dosage: 1 or 2 tablets t.i.d. at mealtime and 2 at bedtime.

Milpath®

®Miltown + *anticholinergic*

WALLACE LABORATORIES *Cranbury, N. J.*

IN CHRONIC,
FUNCTIONAL
CONSTIPATION



DOXIDAN®

THERAPEUTIC GENTLE EFFECTIVE LAXATION DOXIDAN

FOR GENTLE, EFFECTIVE LAXATION

Doxidan is a safe gentle laxative containing a superior fecal softener and the mild peristaltic stimulant, danthron. Because the fecal softener is highly effective, a subclinical dose of danthron is all that is needed to promote easy normal evacuation. Doxidan has been shown to be clinically effective in atonic constipation caused by previous use of harsh cathartics, during pregnancy and the puerperium, and in hemorrhoidal and postoperative conditions where avoidance of straining at stool is desirable.[1,2]

Doxidan effects easy defecation, free of pain, strain and cramping.[1] As a result, "rebound constipation" is largely obviated and the tendency toward laxative dependency is greatly reduced.

FORMULA: Each capsule contains 50 mg. danthron (1, 8-dihydroxyanthraquinone) and 60 mg. calcium bis-(dioctyl sulfosuccinate).

DOSAGE: Adults and children over 12, one or two capsules. Children, age 6 to 12, one capsule. Administered at bedtime for 2 or 3 days or until bowel movements are normal. Supplied in bottles of 30 and 100 soft gelatin capsules.

1. Beil, A. R. and Brevetti, R. E.: Management of constipation during the puerperium, New York State J. Med. 60:2706-2707, September 1, 1960.
2. McCarthy, E. V.: Calcium bis-(dioctyl sulfosuccinate) in treatment of constipation, Clin. Med. 7:2257-2259, November, 1960.

LLOYD BROTHERS, INC.
Cincinnati 29, Ohio